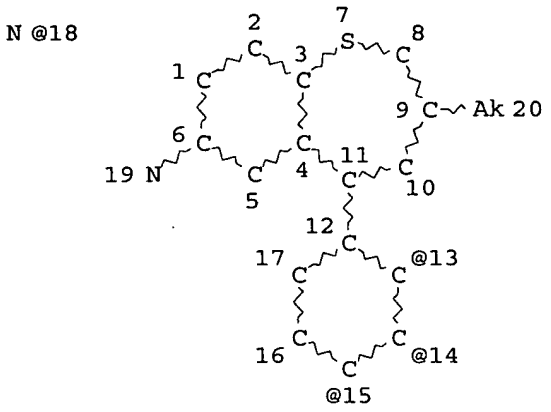
```
=> d his nofil

     (FILE 'HOME' ENTERED AT 16:45:22 ON 05 SEP 2006)

     FILE 'HCAPLUS' ENTERED AT 16:45:32 ON 05 SEP 2006
                E US2003-734787/APPS
L1            1 SEA ABB=ON  PLU=ON  US2003-734787/AP
                SEL RN

     FILE 'REGISTRY' ENTERED AT 16:45:46 ON 05 SEP 2006
L2            6 SEA ABB=ON  PLU=ON  (158736-49-3/BI OR 252047-40-8/BI OR
                263562-55-6/BI OR 338454-52-7/BI OR 57-88-5/BI OR 9028-35-7/BI)

                D SCA

     FILE 'REGISTRY' ENTERED AT 16:46:12 ON 05 SEP 2006
L3              STR
L4            5 SEA SSS SAM L3
L5          141 SEA SSS FUL L3

     FILE 'HCAPLUS' ENTERED AT 16:47:43 ON 05 SEP 2006
L6           15 SEA ABB=ON  PLU=ON  L5

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 16:48:32 ON 05 SEP 2006
L7            0 SEA ABB=ON  PLU=ON  L5

     FILE 'HCAPLUS' ENTERED AT 16:48:40 ON 05 SEP 2006
                E ALZHEIM/CT
                E E5+ALL
                E E2+ALL
L8        23218 SEA ABB=ON  PLU=ON  "ALZHEIMER'S DISEASE"+PFT,NT/CT
L9           15 SEA ABB=ON  PLU=ON  L6 OR (L6 AND (L8 OR ALZHEIM?))
L*** DEL      1 S (L6 AND (L8 OR ALZHEIM?))
L*** DEL      1 S L10 AND L1

     FILE 'HCAPLUS, MEDLINE, EMBASE, BIOSIS' ENTERED AT 16:50:39 ON 05 SEP 2006
                E CANTON T/AU
L10          84 SEA ABB=ON  PLU=ON  ("CANTON T"/AU OR "CANTON THIERRY"/AU)
                E PRADIER L/AU
L11         350 SEA ABB=ON  PLU=ON  ("PRADIER L"/AU OR "PRADIER LAURANT"/AU OR
                "PRADIER LAURENT"/AU)
                E BENAVIDES J/AU
L12         648 SEA ABB=ON  PLU=ON  ("BENAVIDES J"/AU OR "BENAVIDES J A"/AU OR
                "BENAVIDES J B"/AU OR "BENAVIDES J E MAURICIO"/AU OR "BENAVIDES
                 J F"/AU OR "BENAVIDES J G"/AU OR "BENAVIDES J I"/AU OR
                "BENAVIDES J M"/AU OR "BENAVIDES J O"/AU OR "BENAVIDES J R"/AU
                OR "BENAVIDES JESUS"/AU)
                E HEUER H/AU
L13         609 SEA ABB=ON  PLU=ON  ("HEUER H"/AU OR "HEUER H E"/AU OR "HEUER
                H G"/AU OR "HEUER H H"/AU OR "HEUER H J"/AU OR "HEUER H O"/AU
                OR "HEUER H R"/AU OR "HEUER H ROBERT"/AU OR "HEUER H W"/AU OR
                "HEUER HUBERT"/AU OR "HEUER HUBERT O"/AU OR "HEUER HUBERT
                OTTO"/AU)
                E SCHAEFER H/AU
L*** DEL      0 S E3,E24,E40E
L14        1853 SEA ABB=ON  PLU=ON  ("SCHAEFER H"/AU OR "SCHAEFER H L"/AU OR
                "SCHAEFER HANS"/AU OR "SCHAEFER HANS LUDWIG"/AU OR "SCHAEFER
                HANS LUDWING"/AU)
L15          55 SEA ABB=ON  PLU=ON  (L10 AND (L11 OR L12 OR L13 OR L14)) OR
```

```
                (L11 AND (L12 OR L13 OR L14)) OR (L12 AND (L13 OR L14)) OR
                (L13 AND L14)
L16          3484 SEA ABB=ON  PLU=ON  (L10 OR L11 OR L12 OR L13 OR L14)
L17             4 SEA ABB=ON  PLU=ON  L16 AND L5
L18           219 SEA ABB=ON  PLU=ON  L16 AND ALZHEIM?
L19            13 SEA ABB=ON  PLU=ON  L16 AND REUP?
L20             0 SEA ABB=ON  PLU=ON  L18 AND L19
L21            54 SEA ABB=ON  PLU=ON  L16 AND INTEST?
L22             6 SEA ABB=ON  PLU=ON  L16 AND INTEST?(5A) ?INHIB?
L23           519 SEA ABB=ON  PLU=ON  L16 AND INHIB?
L24            69 SEA ABB=ON  PLU=ON  L23 AND (INTEST? OR HMG? OR REDUCTAS? OR
                CHOLEST? OR APP OR SECRETAS? OR REUP? OR BILIAR?)
L25           121 SEA ABB=ON  PLU=ON  L24 OR L22 OR L17 OR L15
L26            65 DUP REM L25 (56 DUPLICATES REMOVED)
                      ANSWERS '1-50' FROM FILE HCAPLUS
                      ANSWERS '51-52' FROM FILE MEDLINE
                      ANSWER '53' FROM FILE EMBASE
                      ANSWERS '54-65' FROM FILE BIOSIS

=> fil hcap
FILE 'HCAPLUS' ENTERED AT 16:59:01 ON 05 SEP 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)


Copyright of the articles to which records in this database refer is
held by the publishers listed in the PUBLISHER (PB) field (available
for records published or updated in Chemical Abstracts after December
26, 1996), unless otherwise indicated in the original publications.
The CA Lexicon is the copyrighted intellectual property of the
the American Chemical Society and is provided to assist you in searching
databases on STN.  Any dissemination, distribution, copying, or storing
of this information, without the prior written consent of CAS, is
strictly prohibited.

FILE COVERS 1907 - 5 Sep 2006  VOL 145 ISS 11
FILE LAST UPDATED: 4 Sep 2006  (20060904/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l9
L3              STR
```



VPA 18-13/14/15 U
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE

```
L5          141 SEA FILE=REGISTRY SSS FUL L3
L6           15 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5
L8        23218 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "ALZHEIMER'S DISEASE"+PFT,NT/C
                T
L9           15 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6 OR (L6 AND (L8 OR ALZHEIM?)
                )
```

=> d l9 ibib abs hitind hitstr 1-15

L9 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN

```
ACCESSION NUMBER:         2005:979630  HCAPLUS
DOCUMENT NUMBER:          143:286456
TITLE:                    Preparation of benzothiazepine and benzothiepine
                          compounds for prevention and treatment of hyperlipemia
INVENTOR(S):              Sasahara, Takehiko; Mohri, Mitsunobu; Kasahara,
                          Kenichi
PATENT ASSIGNEE(S):       Asahi Kasei Pharma Corporation, Japan
SOURCE:                   PCT Int. Appl., 551 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 Japanese
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:
```

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005082874	A1	20050909	WO 2005-JP3686	20050225

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,

NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM,
SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 2004-128992 A 20040227
OTHER SOURCE(S): MARPAT 143:286456
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Benzothiazepine or benzothiepine compds. represented by the following general formula (I) which have a thioamide bond and a quaternary ammonium substituent [R1a, R2a = C1-10 alkyl, C2-10 alkenyl, C2-10 alkynyl; ma = an integer of 0-4; Rx = halo, NO2, NH2, cyano, HO, CO2H, CONH2, SO3H, C1-5 alkylated NH2, each (un)substituted C1-10 alkyl, C2-10 alkenyl, or C2-10 alkynyl; a combination of (A1, A2, A3) = (CH2, NH, CH), (CH2, CH(OH), CH), (NH, CH(OH), CH), or (CH2, CH2, N); Y = NHC(S), NHC(S)NH, NHC(S)O; Za-(N+R5aR6aR7a)n = C2-10 alkyl or alkenyl substituted by n number of (N+R5aR6aR7a) with ≥1 CH2 of Za optionally being replaced with (un)substituted phenylene or O; n = 1,2; N+R5aR6aR7a is selected from (1) R5a, R6a, R7a = each (un)substituted C1-10 alkyl, C2-10 alkenyl, or C2-10 alkynyl with ≥1 CH2 optionally being replaced with phenylene, thienylene, furylene, cyclohexylene, cyclopentylene, O, S, CO2, NHCO, (un)substituted NH, or ammonium ion, (2) C4-9 mono- or bicyclic ring containing ammonium N atom with at least one of the ring C atoms being replaced with O, N, or S, and (3) (un)substituted pyridinium, quinolinium, or isoquinolinium; X- = a counter ion] are prepared These compds. are useful as remedies and preventives for hyperlipemia, arteriosclerosis, syndrome X, and other coronary artery diseases and as cholesterol-lowering agents. They are also useful as remedies and preventives for liver disorders accompanying bile stasis, in particular, primary biliary cirrhosis, and primary sclerotic cholangitis, and obesity, fatty liver, and fatty hepatitis. Thus, 95 mg 1-(4-isocyanatobenzyl)-1-azoniabicyclo[2.2.2]octane bromide (preparation given) was added to a solution of 116 mg 5-(3-aminophenyl)-3,3-dibutyl-7-dimethylamino-4-hydroxy-2,3,4,5-tetrahydro-1-benzothiepin-1,1-dioxide in 3 mL CHCl3 and stirred at 50° for 2 h to give 190 mg -2,3,4,5-tetrahydro-1-benzothiepin-1,1-dioxide derivative (II). II at 0.3 mg/kg twice a day for 5 days lowered a total blood level of LDL and VLDL by 49% in rats on 5 day diet of a feed containing 0.5% cholesterol and 0.5% bile acid.

IC ICM C07D281-10
ICS A61K031-22; A61K031-366; A61K031-38; A61K031-381; A61K031-395; A61K031-4025; A61K031-428; A61K031-439; A61K031-4995; A61K031-5375; A61K031-541; A61K031-554; A61P001-16; A61P003-04; A61P003-06; A61P009-10; C07D337-08; C07D409-12; C07D453-02

CC 28-22 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 27

IT 670276-97-8P 670276-98-9P 670276-99-0P 670277-00-6P 670277-01-7P
670277-13-1P 670277-14-2P 670277-15-3P 670277-16-4P 670277-17-5P
670277-18-6P 670277-19-7P 670277-20-0P 670277-21-1P 670277-22-2P
670277-23-3P 670277-24-4P 670277-25-5P 670277-27-7P 670277-29-9P
670277-30-2P 670277-31-3P 670277-32-4P 670277-33-5P 670277-34-6P

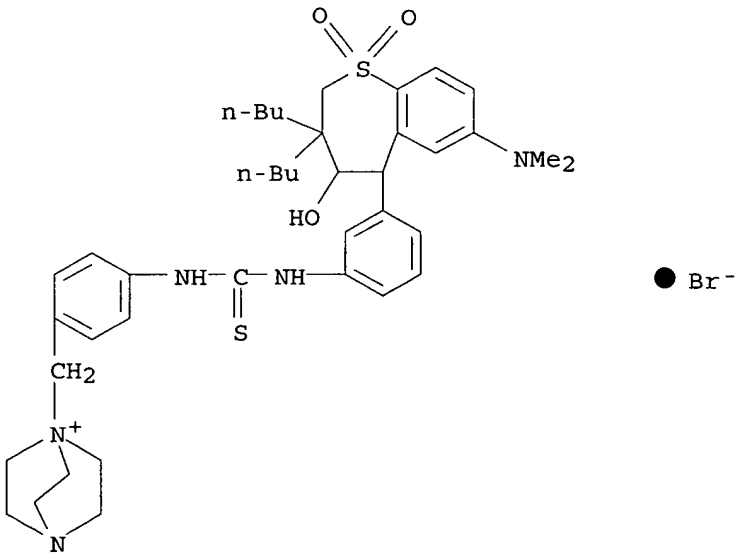
670277-35-7P 670277-36-8P 670277-37-9P 670277-39-1P 670277-40-4P
670277-41-5P 670277-42-6P 670277-43-7P 670277-44-8P 670277-45-9P
670277-46-0P 670277-47-1P 670277-48-2P 670277-49-3P 670277-50-6P
670277-51-7P 670277-52-8P 670277-53-9P 670277-54-0P 670277-55-1P
670277-56-2P 670277-57-3P 670277-58-4P 670277-59-5P 670277-60-8P
670277-61-9P 670277-62-0P 670277-63-1P 670277-64-2P 670277-65-3P
670277-66-4P 670277-68-6P 670277-69-7P 670277-70-0P 670277-71-1P
670277-72-2P 670277-73-3P 670277-74-4P 670277-75-5P 670277-76-6P
670277-77-7P 670277-78-8P 670277-79-9P 670277-80-2P 670278-00-9P
670278-38-3P 670278-39-4P 670278-40-7P 670278-41-8P 670278-42-9P
670278-43-0P 670278-44-1P 670278-45-2P 670278-46-3P 670278-47-4P
670278-48-5P 670278-49-6P 670278-50-9P 670278-51-0P 670278-53-2P
670278-54-3P 670278-55-4P 670278-56-5P 671186-85-9P 671186-87-1P
671187-05-6P 671187-10-3P 671187-14-7P 671187-17-0P 671189-34-7P
864348-68-5P 864348-69-6P 864348-70-9P
864348-71-0P 864348-72-1P 864348-73-2P
864348-74-3P 864348-75-4P 864348-76-5P 864348-77-6P 864348-78-7P
864348-79-8P 864348-80-1P 864348-81-2P 864348-82-3P 864348-83-4P
864348-84-5P 864348-85-6P 864348-86-7P 864348-87-8P 864348-88-9P
864348-89-0P 864348-90-3P 864348-91-4P 864348-92-5P 864348-93-6P
864348-94-7P 864348-95-8P 864348-96-9P 864348-97-0P 864348-98-1P
864348-99-2P 864349-00-8P 864349-01-9P 864349-02-0P 864349-03-1P
864349-04-2P 864349-05-3P 864349-06-4P 864349-07-5P 864349-08-6P
864349-09-7P 864349-10-0P 864349-11-1P 864349-12-2P 864349-13-3P
864349-14-4P 864349-15-5P 864349-16-6P 864349-17-7P 864349-18-8P
864349-19-9P 864349-20-2P 864349-21-3P 864349-22-4P 864349-23-5P
864349-24-6P 864349-25-7P 864349-26-8P 864349-27-9P 864349-28-0P
864349-29-1P 864349-30-4P 864349-31-5P 864349-32-6P 864349-33-7P
864349-34-8P 864349-35-9P 864349-36-0P 864349-37-1P 864349-38-2P
864349-39-3P 864349-40-6P 864349-41-7P 864349-42-8P 864349-43-9P
864349-44-0P 864349-45-1P 864349-46-2P 864349-47-3P 864349-48-4P
864349-49-5P 864349-50-8P 864349-51-9P 864349-52-0P 864349-53-1P
864349-54-2P 864349-55-3P 864349-56-4P 864349-57-5P 864349-58-6P
864349-59-7P 864349-60-0P 864349-61-1P 864349-62-2P 864349-63-3P
864349-64-4P 864349-65-5P 864349-66-6P 864349-67-7P 864349-68-8P
864349-69-9P 864349-70-2P 864349-71-3P 864349-72-4P 864349-73-5P
864349-74-6P 864349-75-7P 864349-76-8P 864349-77-9P 864349-78-0P
864349-79-1P 864349-80-4P 864349-81-5P 864349-82-6P 864349-83-7P
864349-84-8P 864349-85-9P 864349-86-0P 864349-87-1P 864349-88-2P
864349-89-3P 864349-90-6P 864349-91-7P 864349-92-8P 864349-93-9P
864349-94-0P 864349-95-1P 864349-96-2P 864349-97-3P 864349-98-4P
864349-99-5P 864350-00-5P 864350-01-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzothiazepine and benzothiepine compds. for prevention and treatment of hyperlipemia and lowering cholesterol)

IT 727-93-5P, 4-Fluoro-2-(4-methoxybenzoyl)phenol 729-39-5P, 4-Methoxybenzoic acid 4-fluorophenyl ester 6141-45-3P, Methyl 2-amino-2-butylhexanoate 31520-33-9P, 5-Bromopentyl isothiocyanate 31520-34-0P, 6-Bromohexyl isothiocyanate 40216-70-4P, Methyl 2-(benzylideneamino)hexanoate 73674-09-6P, 8-Bromooctanoyl chloride 90331-59-2P, 4-(2-Bromoethyl)phenyl isothiocyanate 105732-43-2P, 2-Aminoheptanoic acid methyl ester hydrochloride 155863-31-3P 155863-32-4P, 4-(Bromomethyl)phenyl isothiocyanate 197378-13-5P 197378-15-7P 197378-16-8P 197378-18-0P 197378-46-4P 288161-81-9P, 2-Amino-2-butylhexanol 300350-05-4P 300350-06-5P 300350-07-6P 300350-08-7P 300350-09-8P 300350-10-1P 393855-85-1P 393855-98-6P 393856-01-4P 670278-59-8P, Methyl 2-(benzylideneamino)-2-butylhexanoate

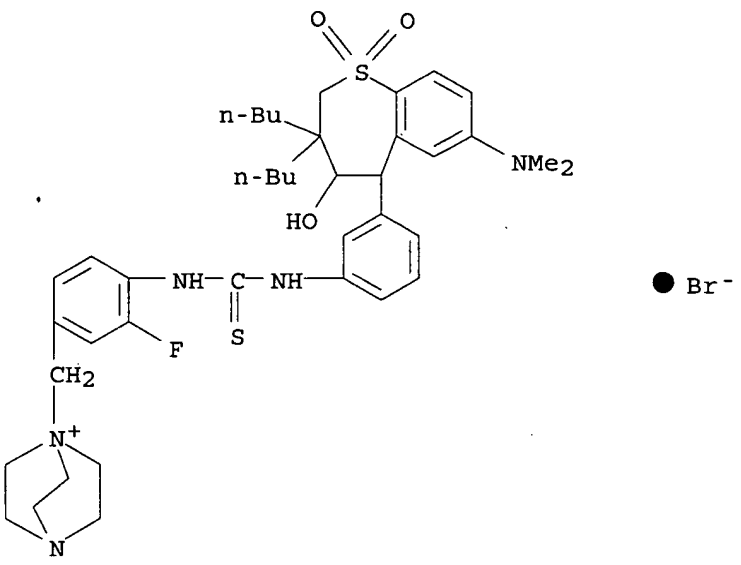
670278-60-1P, 2-[(2-Amino-2-butylhexyl)thio]-5-fluorobenzophenone
670278-61-2P 670278-62-3P 670278-63-4P 670278-65-6P 670278-66-7P
670278-68-9P 670278-69-0P 670278-70-3P 670278-71-4P,
3,3-Dibutyl-2,3-dihydro-7-fluoro-5-(4-methoxyphenyl)-1,4-benzothiazepine-1,1-dioxide 670278-72-5P, 3,3-Dibutyl-2,3-dihydro-7-dimethylamino-5-(4-methoxyphenyl)-1,4-benzothiazepine-1,1-dioxide 670278-73-6P
670278-74-7P 841288-54-8P 864350-02-7P 864350-03-8P 864350-04-9P
864350-05-0P 864350-06-1P 864350-07-2P 864350-08-3P 864350-09-4P
864350-10-7P 864350-11-8P 864350-13-0P **864350-14-1P**
864350-15-2P 864350-16-3P 864350-17-4P 864350-18-5P
864350-19-6P 864350-20-9P 864350-21-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of benzothiazepine and benzothiepine compds. for prevention and treatment of hyperlipemia and lowering cholesterol)

IT **864348-68-5P 864348-69-6P 864348-70-9P**
864348-71-0P 864348-72-1P 864348-73-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzothiazepine and benzothiepine compds. for prevention and treatment of hyperlipemia and lowering cholesterol)

RN 864348-68-5 HCAPLUS
CN 4-Aza-1-azoniabicyclo[2.2.2]octane, 1-[[4-[[[3-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]thioxomethyl]amino]phenyl]methyl]-, bromide (9CI) (CA INDEX NAME)



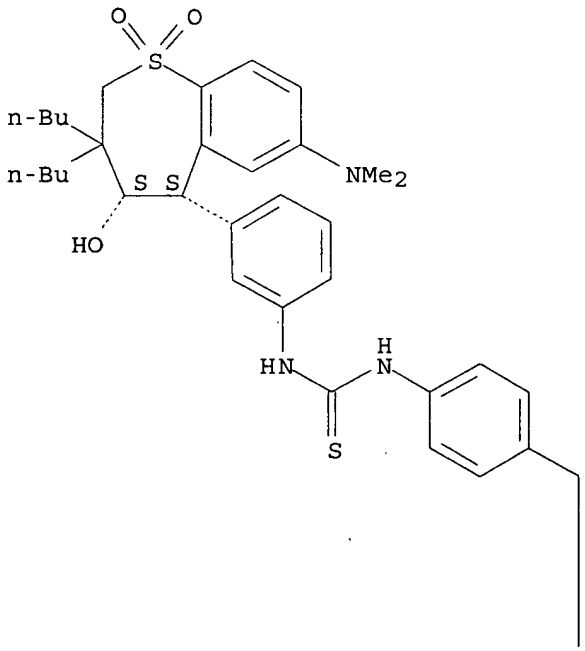
RN 864348-69-6 HCAPLUS
CN 4-Aza-1-azoniabicyclo[2.2.2]octane, 1-[[4-[[[3-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]thioxomethyl]amino]-3-fluorophenyl]methyl]-, bromide (9CI) (CA INDEX NAME)



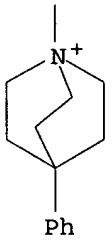
RN 864348-70-9 HCAPLUS
CN 1-Azoniabicyclo[2.2.2]octane, 1-[[4-[[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]thioxomethyl]amino]phenyl]methyl]-4-phenyl-, bromide, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

PAGE 1-A



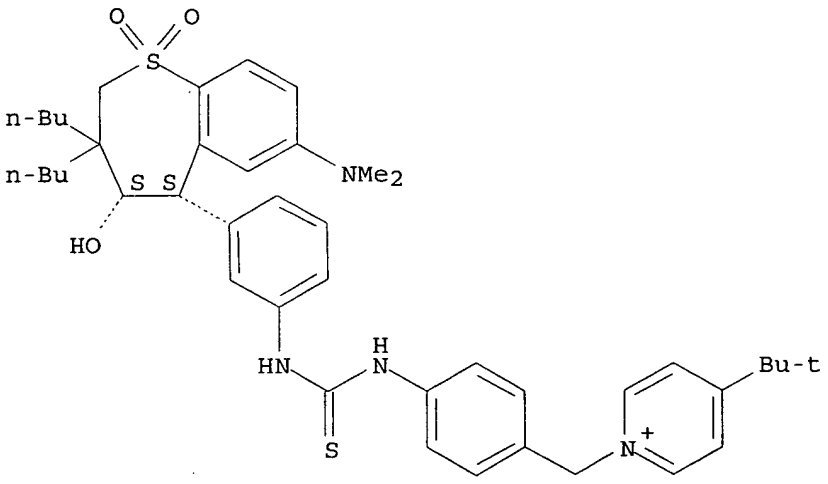
PAGE 2-A



● Br⁻

RN 864348-71-0 HCAPLUS
CN Pyridinium, 1-[[4-[[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]thioxomethyl]amino]phenyl]methyl]-4-(1,1-dimethylethyl)-, bromide, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

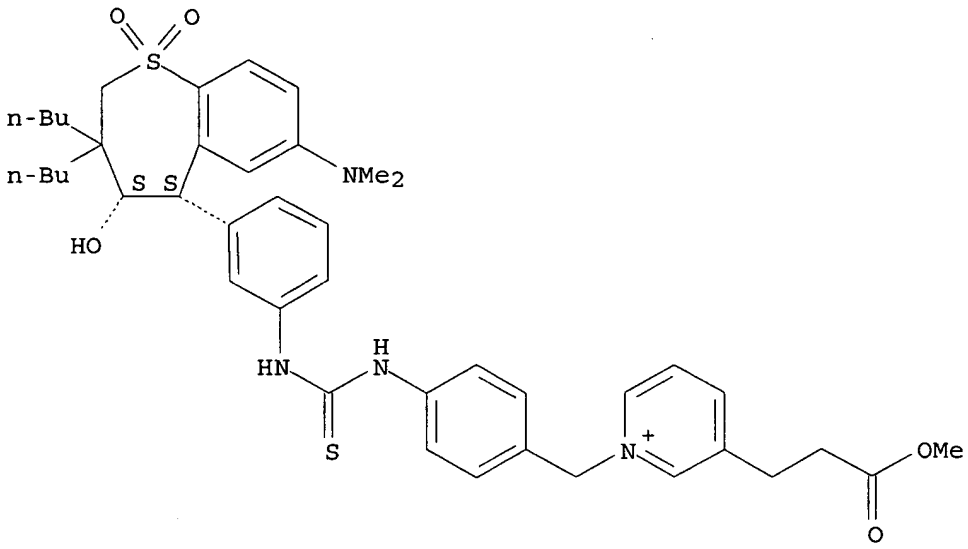


● Br⁻

RN 864348-72-1 HCAPLUS
CN Pyridinium, 1-[[4-[[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]thioxomethyl]amino]phenyl]methyl]-3-(3-methoxy-3-oxopropyl)-, bromide, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

PAGE 1-A



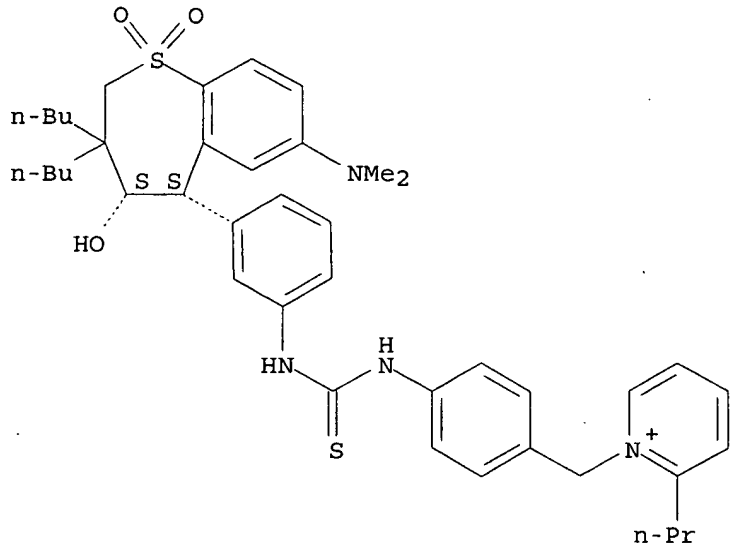
PAGE 2-A

● Br^-

RN 864348-73-2 HCAPLUS
CN Pyridinium, 1-[[4-[[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]thioxomethyl]amino]phenyl]methyl]-2-propyl-, bromide, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

PAGE 1-A

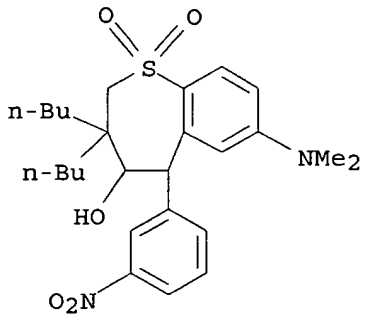


PAGE 2-A

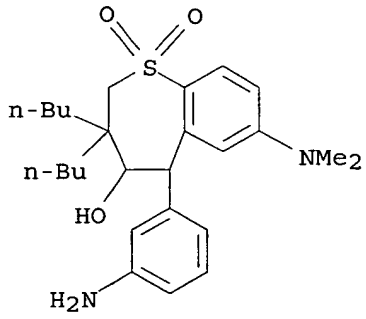
● Br^-

IT **864350-14-1P 864350-15-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of benzothiazepine and benzothiepine compds. for prevention and treatment of hyperlipemia and lowering cholesterol)

RN 864350-14-1 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-, 1,1-dioxide (9CI) (CA INDEX NAME)



RN 864350-15-2 HCAPLUS
CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-, 1,1-dioxide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:704248 HCAPLUS
DOCUMENT NUMBER: 143:347042
TITLE: Discovery of Potent, Nonsystemic Apical Sodium-Codependent Bile Acid Transporter Inhibitors (Part 2)
AUTHOR(S): Huang, Horng-Chih; Tremont, Samuel J.; Lee, Len F.; Keller, Bradley T.; Carpenter, Andrew J.; Wang, Ching-Cheng; Banerjee, Shyamal C.; Both, Scott R.;

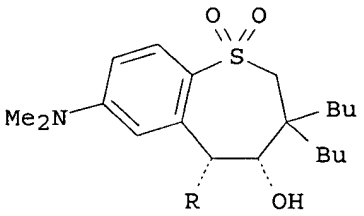
Fletcher, Theresa; Garland, Danny J.; Huang, Wei; Jones, Claude; Koeller, Kevin J.; Kolodziej, Steve A.; Li, James; Manning, Robert E.; Mahoney, Matthew W.; Miller, Raymond E.; Mischke, Deborah A.; Rath, Nigam P.; Reinhard, Emily J.; Tollefson, Michael B.; Vernier, William F.; Wagner, Grace M.; Rapp, Steve R.; Beaudry, Judy; Glenn, Kevin; Regina, Karen; Schuh, Joe R.; Smith, Mark E.; Trivedi, Jay S.; Reitz, David B.

CORPORATE SOURCE: Discovery Chemistry and Department of Cardiovascular Disease, Pharmacia, Chesterfield, MO, 63017, USA

SOURCE: Journal of Medicinal Chemistry (2005), 48(18), 5853-5868
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 143:347042

GI



I

AB Since the primary site for active bile acid reabsorption is via apical sodium-codependent bile acid transporter (ASBT), which is localized on the luminal surface of the distal ileum, a nonsystemic inhibitor would be desirable to minimize or eliminate potential systemic side effects of an absorbed drug. To ensure bioequivalency and product stability, it was also essential that a nonhygroscopic inhibitor in its most stable crystalline form was identified. A series of benzothiepins I [R = Ph, 4-HOC6H4, 4-(Me2NCH2CH2)C6H4, 1-naphthyl, 2-thienyl, 3-pyridyl, etc.] was prepared to refine the structure-activity relationship of the substituted Ph ring at the 5-position of benzothiepin ring and to identify potent, crystalline, nonhygroscopic, and efficacious ASBT inhibitors with low systemic exposure.

CC 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

IT 228113-65-3P 289038-80-8P 865593-98-2P 865593-99-3P 865594-02-1P
865594-03-2P **865594-07-6P 865594-11-2P** 865594-17-8P
865594-23-6P 865594-31-6P 865594-36-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of (aryl)(hydroxy)tetrahydrobenzothiepins as nonsystemic apical sodium-codependent bile acid transporter inhibitors)

IT 197373-42-5P 197373-43-6P 197373-48-1P **197373-51-6P**
197373-56-1P 197373-57-2P 197373-64-1P 197374-40-6P 197374-45-1P
197374-48-4P 197374-67-7P 197374-72-4P 197374-92-8P 197374-96-2P
197375-70-5P 197376-07-1P 197376-11-7P 197376-19-5P 197376-22-0P
197376-34-4P 197376-46-8P 197376-58-2P 197376-67-3P 197376-76-4P
197377-03-0P 197377-38-1P 197377-47-2P 197377-51-8P 197377-62-1P

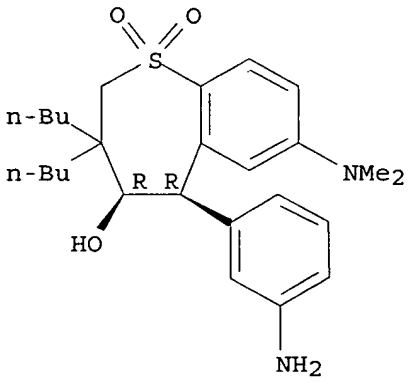
289037-76-9P 865593-97-1P 865594-00-9P 865594-05-4P 865594-06-5P
865594-09-8P 865594-12-3P 865594-14-5P
865594-15-6P 865594-16-7P 865594-18-9P 865594-19-0P 865594-20-3P
865594-22-5P 865594-24-7P 865594-25-8P 865594-26-9P 865594-27-0P
865594-28-1P 865594-29-2P 865594-30-5P 865594-32-7P 865594-33-8P
865594-34-9P 865594-35-0P 865594-37-2P 865594-38-3P 865594-39-4P
865594-40-7P 865594-41-8P 865594-42-9P 865594-43-0P 865594-44-1P
865594-47-4P 865594-48-5P 865594-49-6P 865594-50-9P 865594-52-1P
865594-53-2P 865594-54-3P 865594-55-4P 865594-58-7P 865594-59-8P
865594-60-1P 865594-61-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of (aryl)(hydroxy)tetrahydrobenzothiepins as nonsystemic apical sodium-codependent bile acid transporter inhibitors)

IT 197378-13-5P 197378-15-7P 197378-16-8P 197378-18-0P 289038-53-5P
289038-61-5P 865593-96-0P 865594-01-0P 865594-04-3P
865594-08-7P 865594-10-1P 865594-56-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of (aryl)(hydroxy)tetrahydrobenzothiepins as nonsystemic apical sodium-codependent bile acid transporter inhibitors)

IT **865594-07-6P 865594-11-2P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of (aryl)(hydroxy)tetrahydrobenzothiepins as nonsystemic apical sodium-codependent bile acid transporter inhibitors)

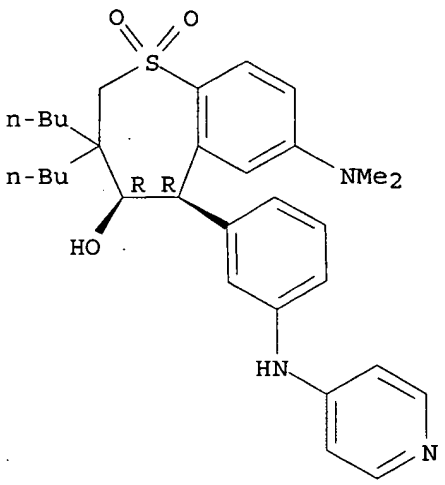
RN 865594-07-6 HCAPLUS
CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 865594-11-2 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-[3-(4-pyridinylamino)phenyl]-, 1,1-dioxide, (4R,5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

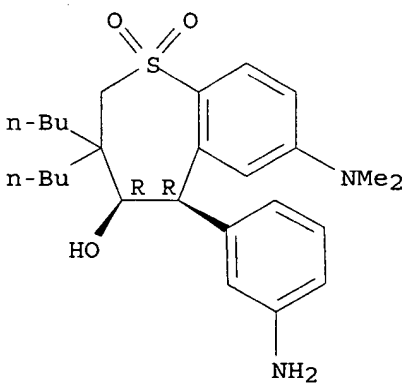


IT **197373-51-6P 865594-09-8P 865594-12-3P**
865594-14-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of (aryl)(hydroxy)tetrahydrobenzothiepins as nonsystemic apical sodium-codependent bile acid transporter inhibitors)

RN 197373-51-6 HCAPLUS

CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

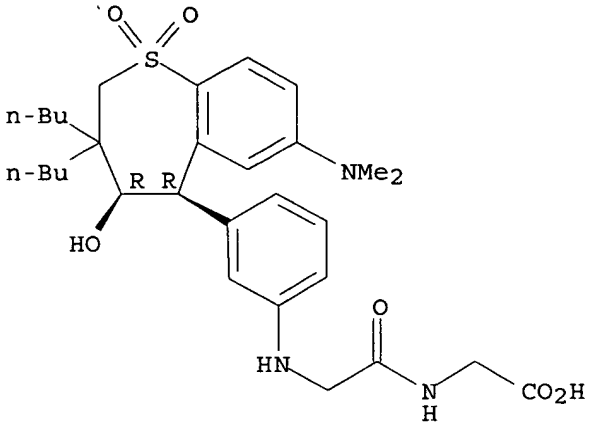
Relative stereochemistry.



RN 865594-09-8 HCAPLUS

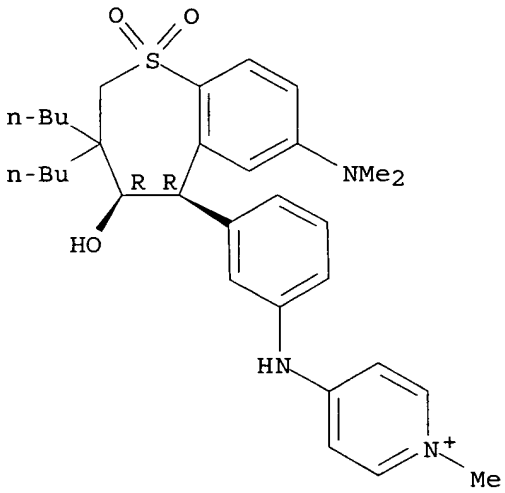
CN Glycine, N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]glycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 865594-12-3 HCAPLUS
CN Pyridinium, 4-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-1-methyl-, iodide (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



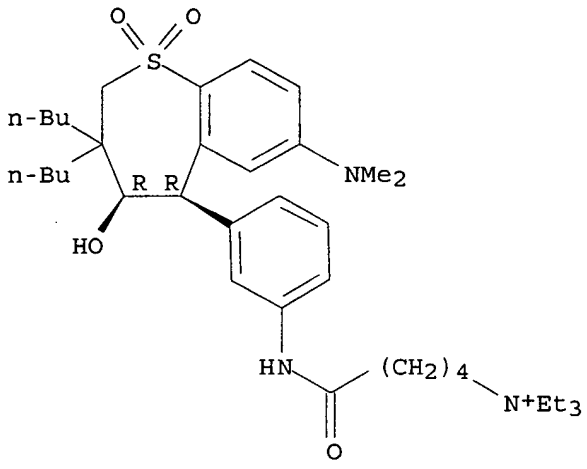
● I^-

RN 865594-14-5 HCAPLUS
CN 1-Pentanaminium, 5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-oxo-, salt with trifluoroacetic acid (1:1) (9CI) (CA INDEX NAME)

CM 1

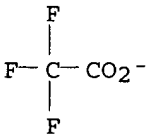
CRN 865594-13-4
CMF C37 H60 N3 O4 S

Absolute stereochemistry. Rotation (+).



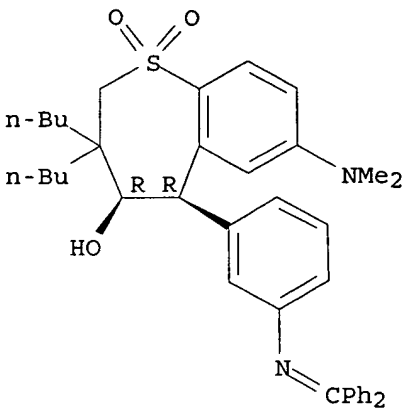
CM 2

CRN 14477-72-6
CMF C2 F3 O2



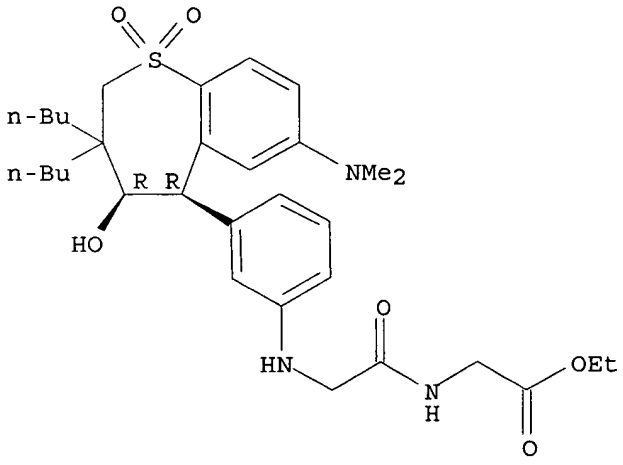
IT **865594-08-7P 865594-10-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of (aryl)(hydroxy)tetrahydrobenzothiepins as nonsystemic apical sodium-codependent bile acid transporter inhibitors)
RN 865594-08-7 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[3-[(diphenylmethylene)amino]phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 865594-10-1 HCAPLUS
CN Glycine, N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]glycyl-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:492306 HCAPLUS
DOCUMENT NUMBER: 141:17641
TITLE: Methods and compositions for the prevention and treatment of **Alzheimer**'s disease with intestinal bile acid reuptake inhibitors
PATENT ASSIGNEE(S): Aventis Pharma SA, Fr.
SOURCE: Fr. Demande, 25 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2848452	A1	20040618	FR 2002-15722	20021212
CA 2507945	AA	20040729	CA 2003-2507945	20031210
WO 2004062652	A1	20040729	WO 2003-FR3654	20031210
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003296802	A1	20040810	AU 2003-296802	20031210
EP 1572174	A1	20050914	EP 2003-815109	20031210
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003017280	A	20051108	BR 2003-17280	20031210
CN 1726016	A	20060125	CN 2003-80105972	20031210
JP 2006514063	T2	20060427	JP 2004-566119	20031210
US 2004138145	A1	20040715	US 2003-734787	20031212
NO 2005003341	A	20050907	NO 2005-3341	20050708
PRIORITY APPLN. INFO.:			FR 2002-15722 A	20021212
			US 2003-455354P P	20030317
			WO 2003-FR3654 W	20031210

OTHER SOURCE(S): MARPAT 141:17641

AB The invention describe the application of the intestinal biliary acid reuptake inhibitors for the prevention and the treatment of **Alzheimer**'s disease, alone or in conjunction with an HMG-CoA reductase inhibitor , a cholesterol uptake inhibitor, a cholesterol synthesis inhibitor or an inhibitor of APP secretases.

IC ICM A61K031-444
ICS A61K031-38; A61P025-28

CC 1-11 (Pharmacology)

ST bile acid reuptake inhibitors intestine **Alzheimers** disease treatment prevention

IT Intestine
(biliary acid reuptake; methods and compns. for prevention and treatment of **Alzheimer**'s disease with intestinal bile acid reuptake inhibitors)

IT **Alzheimer's disease**
Anti-**Alzheimer**'s agents
Human
(methods and compns. for prevention and treatment of **Alzheimer**'s disease with intestinal bile acid reuptake inhibitors)

IT Bile acids
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(reuptake inhibitors; methods and compns. for prevention and treatment of **Alzheimer**'s disease with intestinal bile acid reuptake inhibitors)

IT Biological transport
(reuptake, bile acid, inhibitors of; methods and compns. for prevention and treatment of **Alzheimer**'s disease with intestinal bile acid reuptake inhibitors)

IT Biological transport

(uptake, cholesterol, inhibitors of, in conjunction with treatment; methods and compns. for prevention and treatment of **Alzheimer**'s disease with intestinal bile acid reuptake inhibitors)

IT 9028-35-7, HMG-CoA reductase 158736-49-3, β-Secretase 338454-52-7, γ Secretase
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitor, in conjunction with treatment; methods and compns. for prevention and treatment of **Alzheimer**'s disease with intestinal bile acid reuptake inhibitors)

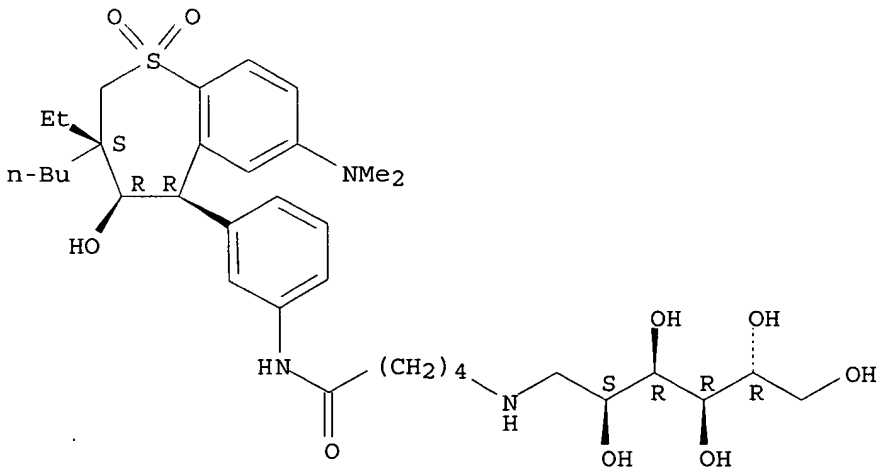
IT **252047-40-8** 263562-55-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and compns. for prevention and treatment of **Alzheimer**'s disease with intestinal bile acid reuptake inhibitors)

IT 57-88-5, Cholesterol, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(uptake and synthesis inhibitors, in conjunction with treatment; methods and compns. for prevention and treatment of **Alzheimer**'s disease with intestinal bile acid reuptake inhibitors)

IT **252047-40-8**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and compns. for prevention and treatment of **Alzheimer**'s disease with intestinal bile acid reuptake inhibitors)

RN 252047-40-8 HCAPLUS
CN D-Glucitol, 1-[[5-[[3-[(3S,4R,5R)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]amino]-1-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:60147 HCAPLUS
DOCUMENT NUMBER: 140:111291
TITLE: Preparation of substituted 5-aryl-benzothiepines as

ileal bile acid transport and taurocholate uptake inhibitors

INVENTOR(S): Lee, Len F.; Banerjee, Shyamal C.; Huang, Horng Chih; Li, Jinglin J.; Miller, Raymond E.; Reitz, David B.; Tremont, Sanuel J.

PATENT ASSIGNEE(S): G.D. Searle and Co., USA

SOURCE: U.S. Pat. Appl. Publ., 235 pp., Cont.-in-part of U.S. Ser. No. 831,284.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 9

PATENT INFORMATION:

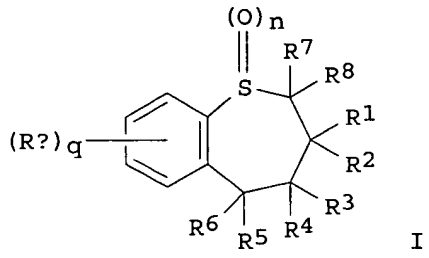
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004014803	A1	20040122	US 2002-68297	20020208
US 6784201	B2	20040831		
CA 2506703	AA	19970918	CA 1997-2506703	19970311
EP 1440972	A1	20040728	EP 2004-10088	19970311
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
AU 761249	B2	20030529	AU 2000-53394	20000816
US 2002013476	A1	20020131	US 2001-828968	20010409
US 6387924	B2	20020514		
US 2003171426	A1	20030911	US 2002-76091	20020215
US 6642268	B2	20031104		
US 2004204478	A1	20041014	US 2004-830125	20040423

PRIORITY APPLN. INFO.:

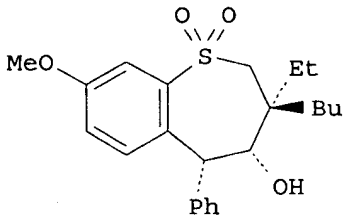
US 1994-305526	B2	19940913
US 1995-517051	B1	19950821
US 1996-13119P	P	19960311
US 1997-816065	A2	19970311
US 1997-831284	A2	19970331
US 2001-828968	A3	20010409
AU 1997-23266	A3	19970311
CA 1997-2248586	A3	19970311
EP 1997-915976	A3	19970311
US 1997-40660P	P	19970311
US 1997-68170P	P	19971219
US 1998-109551	A2	19980702
US 1999-275463	A1	19990324
US 1999-443403	A1	19991119
US 2000-676466	A3	20000929
US 2002-68297	A3	20020208

OTHER SOURCE(S): MARPAT 140:111291

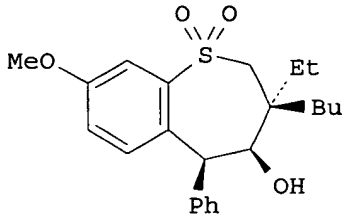
GI



I



II



III

AB The title compds. (I) [wherein q = 1-4; n = 0-2; R1, R2 = H, (un)substituted (halo)alkyl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy(alkyl), dialkylamino, alkylthio, (polyalkyl)aryl, or cycloalkyl; or R1 and R2 taken together with the atoms to which they are attached = cycloalkyl; R3, R4 = H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocyclyl, OR9, NR9R10, SR9, S(O)R9, SO2R9, or SO3R9; R9, R10 = H, (cyclo)alkyl, alkenyl, alkynyl, aryl(alkyl), acyl, heterocyclyl, or ammoniumalkyl; or R3 and R4 together = :O, :NOR11, :S, :NNR11R12, :NR9, or :CR11R12; R11, R12 = H, (cyclo)alkyl, alkenyl, alkynyl, aryl(alkyl), heterocyclyl, carboxylalkyl, carboalkoxyalkyl, cyanoalkyl, OR9, NR9R10, SR9, S(O)R9, SO2R9, SO3R9, CO2R9, CN, halo, oxo, or CONR9R10; R5, R6 = H, alkyl, aryl, etc.; R7, R8 = H, alkyl; Rx = H, (un)substituted (cyclo)alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl(alkyl), halo(alkyl), (quaternary) heterocyclyl, (quaternary) heteroaryl, polyether, alkoxy, amino, alkylthio, NO2, carboxy, carbamido, etc.] were prepared for the prophylaxis and treatment of hyperlipidemic conditions, such as those associated with atherosclerosis or hypercholesterolemia. Thus, KOBu-t was added to a solution of 2-((2-benzyl-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (preparation given) and dry THF cooled to -1.6°C to give, after workup, II and III (96% combined yield). The isomers were separated upon recrystn. II inhibited IBAT-mediated uptake of [14C]-taurocholate in H14 cells with an IC50 of 0.1 μM and reduced serum cholesterol from 143 mg (7%) to 126 mg (2%) compared to control in cholesterol-fed hamsters in a 14-day test. In vitro taurocholate uptake assay data are included for nearly 600 compds. of the invention.

IC ICM C07D337-16
ICS A61K031-38

INCL 514431000; 549012000

CC 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 63

IT 178678-22-3P 178678-23-4P 178678-24-5P 178678-25-6P 178678-26-7P
178678-27-8P 178678-29-0P 178678-33-6P 178678-34-7P 178678-37-0P
178678-46-1P 178678-49-4P 178678-50-7P 178678-51-8P 178678-57-4P
178678-58-5P 178678-59-6P 178897-97-7P 178897-98-8P 178898-00-5P
178898-05-0P 197372-67-1P 197372-71-7P 197372-76-2P 197372-77-3P
197372-78-4P 197373-42-5P 197373-43-6P 197373-44-7P 197373-47-0P
197373-49-2P **197373-50-5P** **197373-51-6P** 197373-55-0P

197373-56-1P 197373-57-2P 197373-58-3P 197375-48-7P 197375-49-8P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

IT 178678-28-9P 178678-30-3P 178678-31-4P 178678-35-8P 178678-36-9P
178678-39-2P 178678-40-5P 178678-41-6P 178678-42-7P 178678-43-8P
178678-44-9P 178678-45-0P 178678-47-2P 178678-48-3P 178678-52-9P
178678-53-0P 178678-54-1P 178897-95-5P 178897-96-6P 178897-99-9P
178898-01-6P 178898-02-7P 178898-03-8P 178898-04-9P 197372-66-0P
197372-69-3P 197372-70-6P 197372-72-8P 197372-73-9P 197372-74-0P
197372-75-1P 197372-79-5P 197372-80-8P 197372-81-9P 197372-82-0P
197372-83-1P 197372-84-2P 197372-85-3P 197372-86-4P 197372-87-5P
197372-88-6P 197372-89-7P 197372-90-0P 197372-91-1P 197372-92-2P
197372-93-3P 197372-94-4P 197372-95-5P 197372-96-6P 197372-97-7P
197372-98-8P 197372-99-9P 197373-00-5P 197373-01-6P 197373-02-7P
197373-03-8P 197373-04-9P 197373-05-0P 197373-06-1P 197373-07-2P
197373-08-3P 197373-09-4P 197373-10-7P 197373-11-8P 197373-12-9P
197373-13-0P 197373-14-1P 197373-16-3P 197373-17-4P 197373-18-5P
197373-19-6P 197373-20-9P 197373-22-1P 197373-24-3P 197373-25-4P
197373-26-5P 197373-27-6P 197373-28-7P 197373-29-8P 197373-30-1P
197373-35-6P 197373-36-7P **197373-37-8P** 197373-38-9P
197373-39-0P 197373-40-3P 197373-41-4P 197373-45-8P 197373-48-1P
197373-54-9P 197373-59-4P 197373-60-7P 197373-61-8P
197373-62-9P 197373-63-0P 197373-64-1P 197373-66-3P 197373-67-4P
197373-68-5P 197373-69-6P 197373-70-9P 197373-71-0P 197373-72-1P
197373-73-2P 197373-75-4P 197373-76-5P 197373-77-6P 197373-78-7P
197373-79-8P 197373-80-1P 197373-81-2P 197373-83-4P 197373-85-6P
197373-87-8P 197373-90-3P 197373-93-6P 197373-95-8P 197373-97-0P
197373-99-2P 197374-00-8P 197374-01-9P 197374-02-0P 197374-03-1P
197374-04-2P 197374-06-4P 197374-08-6P 197374-09-7P
197374-10-0P 197374-11-1P 197374-13-3P 197374-14-4P 197374-16-6P
197374-17-7P 197374-18-8P 197374-19-9P 197374-20-2P 197374-21-3P
197374-22-4P 197374-24-6P 197374-25-7P 197374-26-8P 197374-27-9P
197374-29-1P 197374-30-4P 197374-31-5P 197374-32-6P 197374-34-8P
197374-35-9P 197374-37-1P 197374-38-2P 197374-39-3P 197374-40-6P
197374-41-7P 197374-43-9P 197374-44-0P 197374-45-1P 197374-46-2P
197374-47-3P 197374-48-4P 197374-49-5P 197374-50-8P 197374-51-9P
197374-52-0P 197374-53-1P 197374-54-2P 197374-55-3P 197374-56-4P
197374-57-5P 197374-58-6P **197374-59-7P** 197374-60-0P
197374-62-2P 197374-63-3P 197374-64-4P 197374-65-5P 197374-66-6P
197374-67-7P 197374-68-8P 197374-69-9P 197374-71-3P 197374-72-4P
197374-73-5P 197374-74-6P 197374-75-7P 197374-76-8P 197374-77-9P
197374-78-0P 197374-79-1P 197374-80-4P 197374-81-5P 197374-82-6P
197374-83-7P 197374-84-8P 197374-85-9P 197374-86-0P 197374-87-1P
197374-88-2P 197374-89-3P 197374-90-6P 197374-91-7P 197374-92-8P
197374-93-9P 197374-94-0P 197374-95-1P 197374-96-2P 197374-97-3P
197374-98-4P 197374-99-5P 197375-00-1P 197375-01-2P 197375-02-3P
197375-03-4P 197375-04-5P 197375-05-6P 197375-06-7P 197375-07-8P
197375-08-9P 197375-09-0P 197375-10-3P 197375-11-4P 197375-12-5P
197375-13-6P 197375-14-7P 197375-15-8P 197375-16-9P 197375-17-0P
197375-20-5P 197375-22-7P 197375-23-8P 197375-24-9P 197375-25-0P
197375-26-1P 197375-28-3P 197375-30-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by

cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

IT 197375-32-9P 197375-34-1P 197375-39-6P 197375-42-1P 197375-44-3P
197375-52-3P 197375-57-8P 197375-60-3P 197375-63-6P 197375-66-9P
197375-68-1P 197375-70-5P 197375-72-7P 197375-74-9P 197375-75-0P
197375-80-7P 197375-82-9P 197375-84-1P 197375-86-3P 197375-89-6P
197375-93-2P 197375-94-3P **197375-96-5P** 197375-98-7P
197376-00-4P 197376-02-6P 197376-04-8P 197376-06-0P 197376-07-1P
197376-08-2P 197376-09-3P 197376-10-6P 197376-11-7P 197376-12-8P
197376-13-9P 197376-14-0P 197376-15-1P 197376-17-3P 197376-18-4P
197376-19-5P 197376-21-9P 197376-22-0P 197376-25-3P 197376-31-1P
197376-32-2P 197376-34-4P 197376-36-6P 197376-38-8P 197376-40-2P
197376-42-4P 197376-46-8P 197376-49-1P 197376-52-6P
197376-55-9P 197376-58-2P 197376-61-7P 197376-64-0P
197376-67-3P 197376-69-5P 197376-73-1P 197376-74-2P 197376-75-3P
197376-76-4P 197376-77-5P 197376-78-6P 197376-79-7P 197376-81-1P
197376-82-2P 197376-83-3P 197376-84-4P 197376-85-5P 197376-86-6P
197376-88-8P 197376-89-9P 197376-90-2P 197376-92-4P 197376-94-6P
197376-95-7P 197376-97-9P 197376-99-1P 197377-00-7P 197377-02-9P
197377-03-0P 197377-05-2P 197377-09-6P 197377-10-9P 197377-11-0P
197377-12-1P 197377-14-3P 197377-16-5P 197377-17-6P 197377-18-7P
197377-19-8P 197377-20-1P 197377-21-2P 197377-22-3P 197377-23-4P
197377-24-5P 197377-25-6P 197377-26-7P 197377-27-8P 197377-28-9P
197377-29-0P 197377-30-3P 197377-31-4P 197377-32-5P 197377-33-6P
197377-34-7P 197377-35-8P 197377-36-9P 197377-37-0P 197377-38-1P
197377-39-2P 197377-40-5P 197377-42-7P 197377-43-8P 197377-45-0P
197377-46-1P 197377-47-2P 197377-48-3P 197377-49-4P 197377-50-7P
197377-51-8P 197377-53-0P 197377-54-1P 197377-55-2P 197377-57-4P
197377-58-5P 197377-60-9P 197377-61-0P 197377-62-1P 197377-63-2P
197377-64-3P 197377-65-4P 197377-66-5P 197377-68-7P 197377-69-8P
197377-70-1P 197377-71-2P 197377-72-3P 197377-73-4P 197377-74-5P
197377-75-6P 197377-76-7P 197377-77-8P 197377-78-9P 197377-79-0P
197377-81-4P 197377-82-5P 197377-83-6P 197377-84-7P 197377-85-8P
197377-86-9P 197377-90-5P 197377-94-9P 197377-96-1P 197377-98-3P
197384-36-4P 197384-39-7P 197390-49-1P 197390-68-4P
213312-50-6P 213312-80-2P 213312-99-3P 213313-15-6P 213313-34-9P
213386-72-2P 228113-66-4P 289037-53-2P 289037-54-3P 289037-55-4P
289037-56-5P 289037-57-6P 289037-58-7P 289037-59-8P 289037-60-1P
289037-61-2P 289037-62-3P 289037-64-5P 289037-65-6P 289037-67-8P
289037-68-9P 289037-70-3P 289037-72-5P 289037-74-7P 289037-75-8P
289037-76-9P 289037-77-0P 289037-78-1P 289037-79-2P 289037-80-5P
289037-81-6P 289037-82-7P 289037-83-8P 289037-84-9P 289037-85-0P
289037-86-1P 289037-87-2P 289037-88-3P 289037-90-7P 289037-91-8P
289037-92-9P 289037-93-0P 289037-94-1P 289037-95-2P 289038-00-2P
289038-01-3P 289038-02-4P 289038-03-5P 289038-04-6P 289038-05-7P
289038-06-8P 289038-07-9P 289038-09-1P 289038-11-5P 289038-13-7P
289038-15-9P 289038-16-0P 289038-18-2P 289038-19-3P 289038-21-7P
289038-23-9P 289038-24-0P 289038-25-1P **289038-26-2P**
289038-27-3P **289038-28-4P** 289038-29-5P 289038-30-8P
289038-32-0P 289038-33-1P 289038-34-2P **289038-35-3P**
289038-36-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

IT **289038-37-5P** **289038-38-6P** 289038-39-7P 289038-40-0P
289038-41-1P 289038-42-2P **289038-43-3P** 289038-44-4P

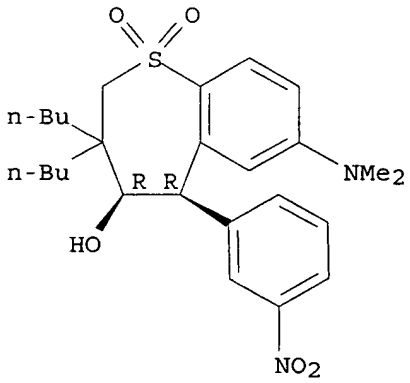
289038-45-5P 289056-45-7P 289056-46-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

IT **197373-53-8P** 280105-79-5P 280105-80-8P 280105-82-0P
280105-83-1P 280105-84-2P 280105-91-1P 280105-92-2P 280105-94-4P
280105-98-8P 280106-01-6P 280106-02-7P 280106-04-9P
280106-05-0P 280106-06-1P 280106-08-3P 280106-09-4P 280106-10-7P
280106-11-8P 280106-12-9P 289039-86-7P 289039-87-8P 289039-88-9P
289039-90-3P 289039-91-4P 289039-93-6P 289039-95-8P 289039-96-9P
289039-97-0P 289039-98-1P 289039-99-2P 289040-00-2P 289040-01-3P
647859-03-8P 647859-04-9P 647859-05-0P **647859-06-1P**
647859-07-2P 647859-08-3P 647859-09-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

IT **197373-50-5P 197373-51-6P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

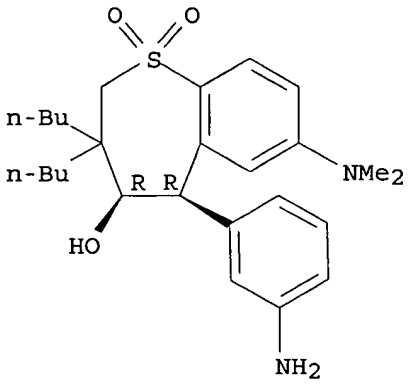
RN 197373-50-5 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 197373-51-6 HCAPLUS
CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

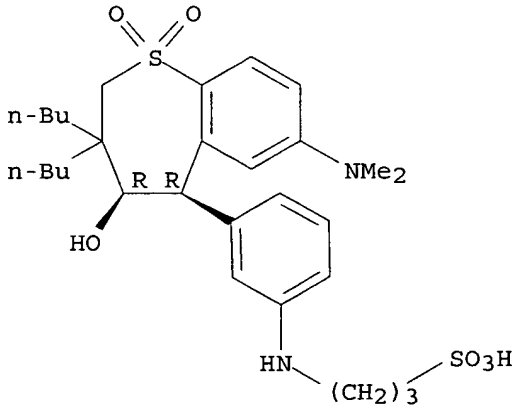


IT **197373-37-8P 197373-54-9P 197374-04-2P**
197374-59-7P 197375-96-5P 197376-42-4P
197376-55-9P 197384-36-4P 289038-26-2P
289038-27-3P 289038-28-4P 289038-35-3P
289038-36-4P 289038-37-5P 289038-38-6P
289038-43-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

RN 197373-37-8 HCAPLUS

CN 1-Propanesulfonic acid, 3-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



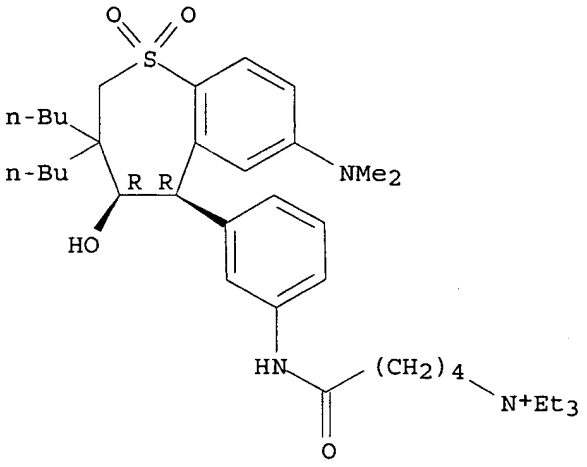
RN 197373-54-9 HCAPLUS

CN 1-Pentanaminium, 5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-oxo-, rel-, salt with trifluoroacetic acid (1:1) (9CI) (CA INDEX NAME)

CM 1

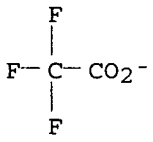
CRN 197373-53-8
CMF C37 H60 N3 O4 S

Relative stereochemistry.



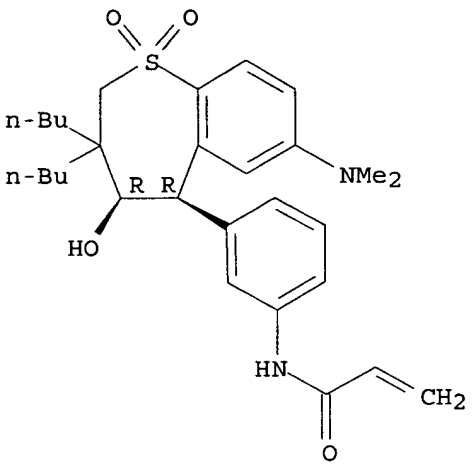
CM 2

CRN 14477-72-6
CMF C2 F3 O2



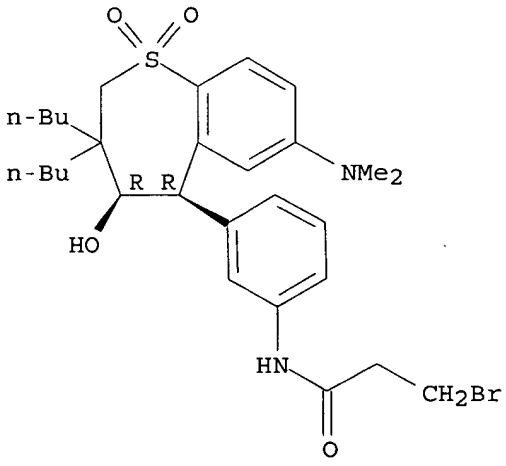
RN 197374-04-2 HCAPLUS
CN 2-Propenamide, N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



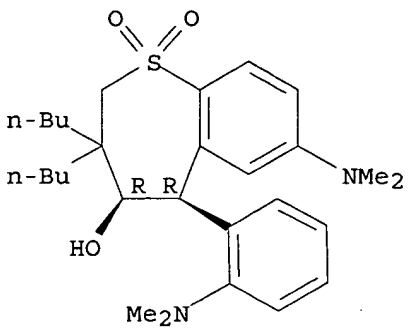
RN 197374-59-7 HCAPLUS
CN Propanamide, 3-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



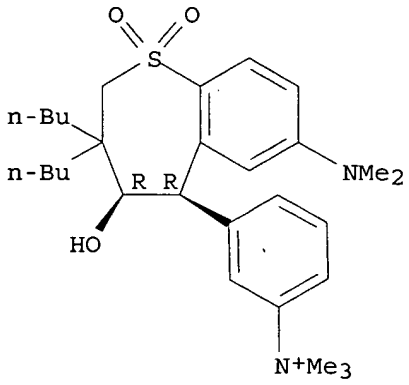
RN 197375-96-5 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[2-(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 197376-42-4 HCAPLUS
CN Benzenaminium, 3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]-N,N,N-trimethyl-, iodide, rel- (9CI) (CA INDEX NAME)

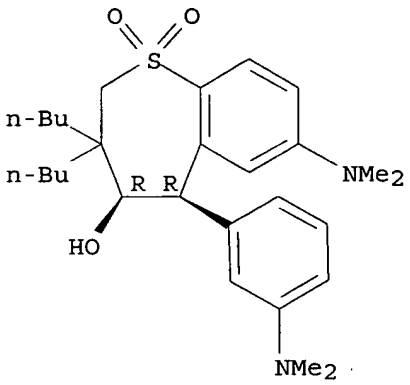
Relative stereochemistry.



● I⁻

RN 197376-55-9 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[3-(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

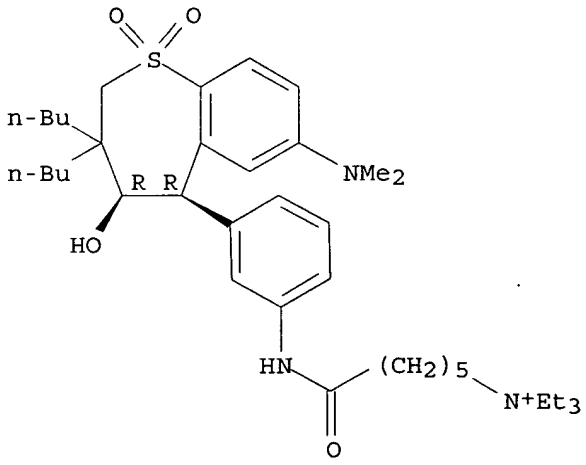


RN 197384-36-4 HCAPLUS
CN 1-Hexanaminium, 6-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-6-oxo-, rel-, salt with trifluoroacetic acid (1:1) (9CI) (CA INDEX NAME)

CM 1

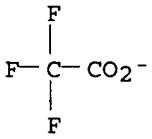
CRN 197384-35-3
CMF C38 H62 N3 O4 S

Relative stereochemistry.



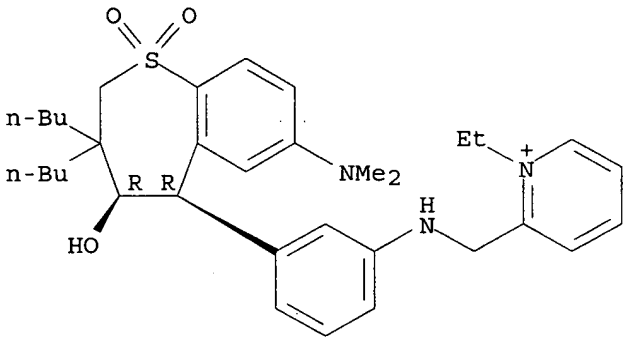
CM 2

CRN 14477-72-6
CMF C2 F3 O2



RN 289038-26-2 HCAPLUS
CN Pyridinium, 2-[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]methyl]-1-ethyl-, iodide, rel- (9CI) (CA INDEX NAME)

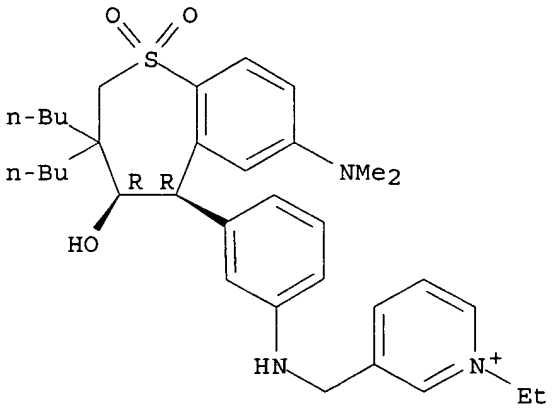
Relative stereochemistry.



● I^-

RN 289038-27-3 HCAPLUS
CN Pyridinium, 3-[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]methyl]-1-ethyl-, iodide, rel- (9CI) (CA INDEX NAME)

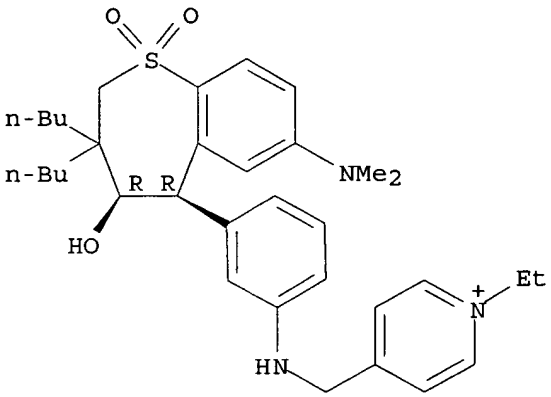
Relative stereochemistry.



● I^-

RN 289038-28-4 HCAPLUS
CN Pyridinium, 4-[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]methyl]-1-ethyl-, iodide, rel- (9CI) (CA INDEX NAME)

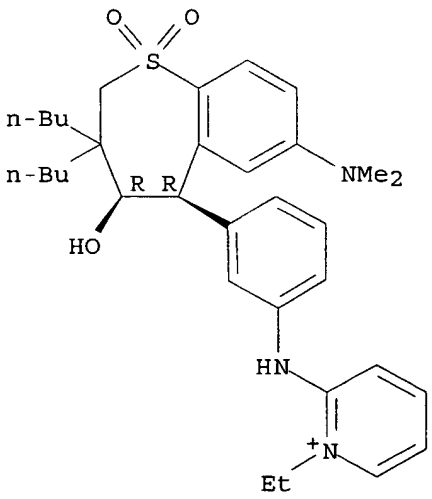
Relative stereochemistry.



● I⁻

RN 289038-35-3 HCAPLUS
CN Pyridinium, 2-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-1-ethyl-, iodide, rel- (9CI) (CA INDEX NAME)

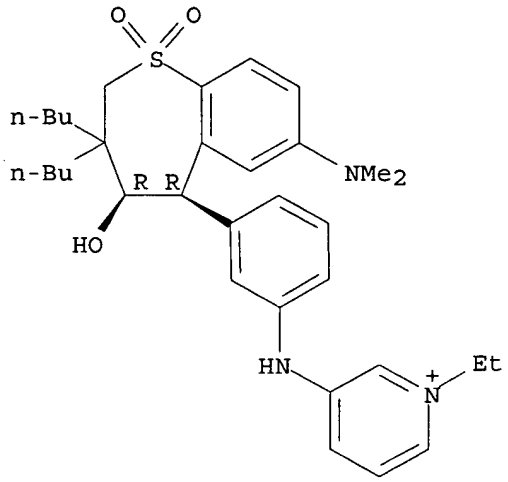
Relative stereochemistry.



● I⁻

RN 289038-36-4 HCAPLUS
CN Pyridinium, 3-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-1-ethyl-, iodide, rel- (9CI) (CA INDEX NAME)

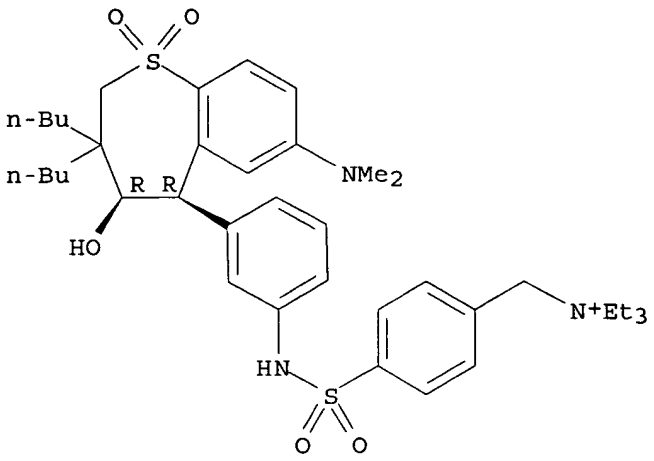
Relative stereochemistry.



● I^-

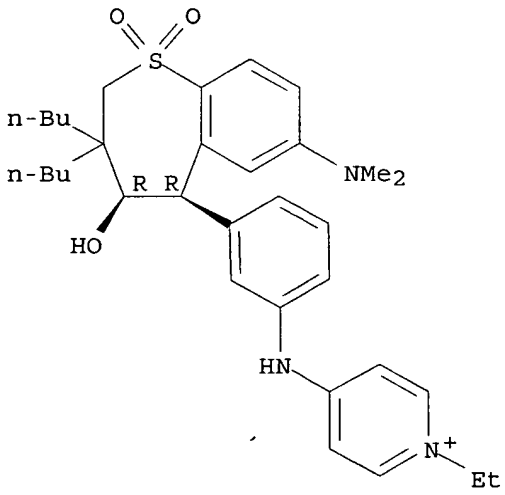
RN 289038-37-5 HCAPLUS
CN Benzenemethanaminium, 4-[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]sulfonyl]-N,N,N-triethyl-, iodide, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



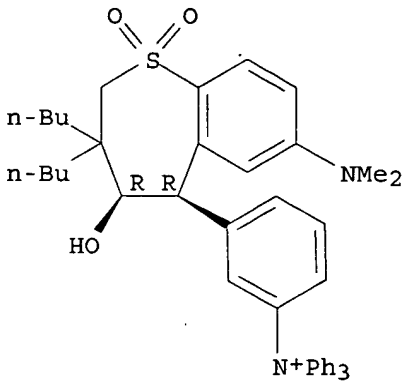
RN 289038-38-6 HCAPLUS
CN Pyridinium, 4-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-1-ethyl-, iodide, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 289038-43-3 HCAPLUS
CN Benzenaminium, 3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]-N,N,N-triphenyl-, bromide, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



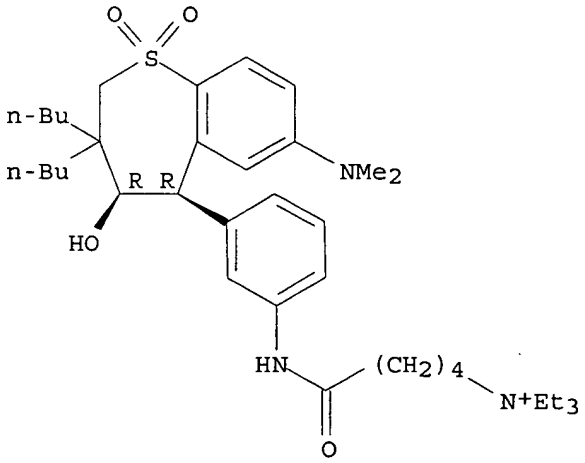
● Br^-

IT **197373-53-8P 280105-98-8P 647859-06-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

RN 197373-53-8 HCAPLUS

CN 1-Pentanaminium, 5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-oxo-, rel- (9CI) (CA INDEX NAME)

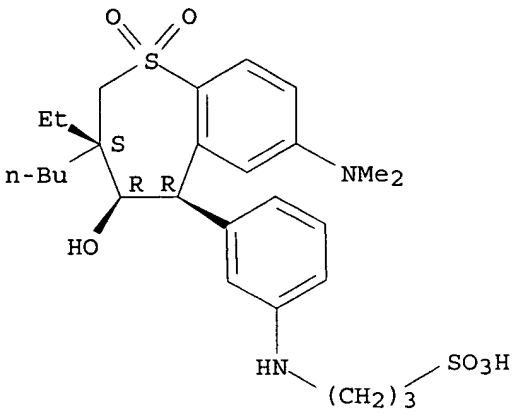
Relative stereochemistry.



RN 280105-98-8 HCAPLUS

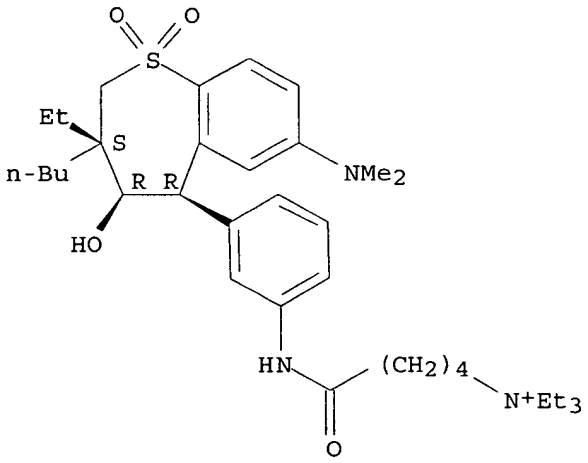
CN 1-Propanesulfonic acid, 3-[[3-[(3R,4S,5S)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 647859-06-1 HCAPLUS
CN 1-Pentanaminium, 5-[[3-[(3R,4S,5S)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-oxo-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



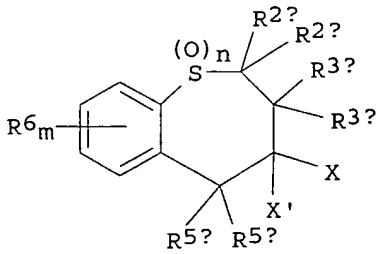
REFERENCE COUNT: 231 THERE ARE 231 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:376848 HCAPLUS
DOCUMENT NUMBER: 138:385315
TITLE: Mono- and di-fluorinated benzothiepines as inhibitors of apical sodium co-dependent bile acid transport (ASBT) and taurocholate uptake for treating hyperlipidemic conditions and methods for preparation
INVENTOR(S): Koeller, Kevin J.; Tremont, Samuel J.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA

SOURCE: PCT Int. Appl., 589 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003040127	A1	20030515	WO 2002-US35257	20021104
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2464685	AA	20030515	CA 2002-2464685	20021104
US 2004067872	A1	20040408	US 2002-286987	20021104
US 6740663	B2	20040525		
BR 2002013501	A	20040824	BR 2002-13501	20021104
EP 1448546	A1	20040825	EP 2002-778711	20021104
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2005518347	T2	20050623	JP 2003-542173	20021104
US 2004176438	A1	20040909	US 2003-743404	20031223
PRIORITY APPLN. INFO.:			US 2001-330892P	P 20011102
			US 2002-286987	A3 20021104
			WO 2002-US35257	W 20021104

OTHER SOURCE(S): MARPAT 138:385315
GI



I

AB Mono-fluorinated and di-fluorinated benzothiepine apical Na co-dependent bile acid transport (ASBT) inhibitors (shown as I; variables defined below; no specific examples are included) are disclosed together with methods of making the same, methods of using the same to treat hyperlipidemic conditions as well as pharmaceutical compns. containing the same compds. For I: X = F, X' = H, F; n = 0-2; m = 0-4; R2A and R2B = H and hydrocarbyl; R3A, R3B, R5A, and R5B = H, alkyl, cycloalkyl, alkenyl, alkynyl, heterocyclyl, quaternary heterocyclyl, oxo, aryl-R5, -OR9, -NR9R10, -SR9, -S(O)R9, -SO2R9, and -SO3R9; R9 and R10 = H, hydrocarbyl, amino, and hydrocarbylamino. R5 = H, hydrocarbyl, heterocyclyl,

quaternary heterocyclyl, -OR9, -SR9, -S(O)R9, -SO2R9, and -SO3R9; ≥1 R6 radicals = H, halogen, -CN, -NO2, hydrocarbyl, -R5, -OR13, -NR 13R14, -SR13, -S(O)R13, -S(O)2R13, -SO3R13, -S+R3R14A-, -NR13OR14, -NR13NR14R15, -OM, -SO2OM, -SO2NR13R14, -NR14C(O)R13, -C(O)OM, -S(O)NR13R14, -N+R13R14R15A-, -PR13R14, -P(O)R13R4, -P+R13R14R15A-, amino acid residue, peptide residue, polypeptide residue, and carbohydrate residue; addnl. details are given in the claims. I (X = X' = F) are claimed to be preparable from the 4-oxo analog and diethylaminosulfur trifluoride; I (X = F; X' = H) are claimed preparable from the 4-hydroxy analog and diethylaminosulfur trifluoride. Hundreds of example prepns. of precursors to I are included, but none of I; most of the example prepns. have appeared in earlier patents (e.g. WO 98/40375). Biol. testing procedures are described but no test results are reported except for the statement that a polyethylene glycol-functionalized benzothiepine (4500 MW; a 4-hydroxy analog of I) inhibited ileal bile acid transport-mediated uptake of 14C-taurocholate in H14 cells.

IC ICM C07D337-00
ICS A61K031-38

CC 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

IT 1426-54-6P, 4-Fluoro-2-[(4-methoxyphenyl)methyl]phenol 1481-12-5P, 4-Fluoro-2-(4'-fluorobenzyl)phenol 1515-89-5P, 3-Bromobenzyl methyl ether 3670-91-5P 15886-84-7P 16473-35-1P, 1-(Chloromethyl)-4-(hydroxymethyl)benzene 24632-01-7P, 1-(Hydroxymethyl)cyclohexanecarboxaldehyde 24765-57-9P, 2,2-Dibutyl-1,3-propanediol 70132-87-5P 120454-34-4P, 2-Mercaptodiphenylmethane 120936-00-7P, O-2-Benzylphenyl dimethylthiocarbamate 120936-01-8P 131117-88-9P 162632-54-4P, 2-Mercapto-4-methoxybenzophenone 163445-43-0P, 2-Mercapto-5-methoxybenzophenone 174747-95-6P, 1-Bromo-2-butyl-2-(hydroxymethyl)hexane 178678-21-2P 178678-22-3P, 3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepine 178678-23-4P, cis-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-4(5H)-one 178678-24-5P, trans-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-4(5H)-one 178678-25-6P, cis-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-4(5H)-one-1,1-dioxide 178678-26-7P 178678-27-8P 178678-29-0P 178678-33-6P, 3-Ethyl-5-phenyl-2,3-dihydrobenzothiepine 178678-34-7P 178678-36-9P, cis-3-Ethyl-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide 178678-37-0P 178678-40-5P 178678-45-0P 178678-46-1P 178678-49-4P 178678-50-7P 178678-51-8P 178678-55-2P 178678-56-3P, 2-[(2-Benzoylphenylthio)methyl]-2-ethylhexanal 178678-57-4P, 2-[(2-Benzoylphenylthio)methyl]butyraldehyde 178678-58-5P 178678-59-6P 178678-60-9P 178678-61-0P 178678-62-1P 178678-63-2P 178678-64-3P 178678-65-4P 178678-66-5P 178678-67-6P 178678-68-7P 178678-69-8P 178678-70-1P 178678-71-2P 178678-72-3P 178678-73-4P 178897-97-7P 178898-00-5P 178898-01-6P 178898-05-0P 197372-67-1P 197372-71-7P 197372-76-2P 197372-77-3P 197372-78-4P 197373-02-7P 197373-03-8P 197373-13-0P 197373-42-5P 197373-43-6P 197373-44-7P 197373-46-9P 197373-47-0P 197373-49-2P **197373-50-5P 197373-51-6P 197373-52-7P** 197373-55-0P 197373-56-1P 197373-57-2P 197373-58-3P 197377-84-7P 197378-05-5P 197378-07-7P, 4-Chloro-3-(4-methoxyphenylmethyl)nitrobenzene 197378-15-7P 197378-16-8P 197378-18-0P 197378-20-4P 197378-22-6P 197378-24-8P 197378-26-0P 197378-29-3P 197378-31-7P 197378-32-8P 197378-34-0P 197378-36-2P 197378-38-4P 197378-40-8P 197378-42-0P 197378-44-2P 197378-46-4P 197378-48-6P, 4-Fluoro-2-(3'-methoxybenzyl)phenol 197378-50-0P 197378-52-2P 197378-54-4P 197378-56-6P 197378-58-8P 228113-57-3P 228113-58-4P 228113-59-5P 228113-63-1P 228113-64-2P 270931-13-0P 270931-14-1P 270931-15-2P 288863-77-4P **289037-96-3P 289037-98-5P** 289038-46-6P 289038-47-7P

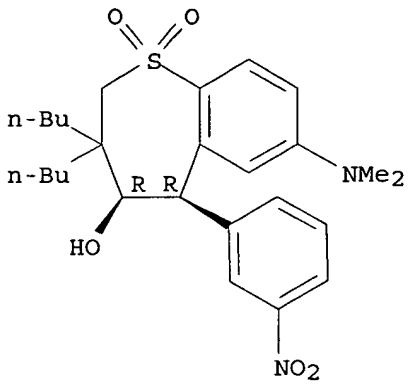
289038-49-9P 289038-51-3P 289038-52-4P 289038-53-5P 289038-54-6P
289038-55-7P 289038-56-8P 289038-57-9P 289038-58-0P 289038-59-1P
289038-60-4P 289038-61-5P 289038-63-7P 289038-64-8P 289038-65-9P
289038-66-0P 289038-68-2P 289038-69-3P 289038-70-6P 289038-72-8P
289038-74-0P 289038-75-1P 289038-77-3P 289038-78-4P 289038-79-5P
289038-80-8P 289038-81-9P 289038-82-0P 289038-83-1P 289038-84-2P
289038-86-4P 289038-87-5P 361373-66-2P, 2-(Bromomethyl)-2-butylhexanal
361374-22-3P 361374-31-4P, 3-Acetoxy-2,2-dibutyl-1-propanol
525589-60-0P 525589-61-1P 525589-62-2P 525589-63-3P 525589-64-4P
525589-65-5P, 4-Methyl-2-(4'-fluorobenzyl)phenol 525589-69-9P
525589-71-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of precursors of mono- and di-fluorinated benzothiepine inhibitors of apical sodium co-dependent bile acid transport (ASBT) and taurocholate uptake for treating hyperlipidemic conditions)

IT 178678-28-9P, 3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepine-1,1-dioxide 178678-30-3P, cis-3-Butyl-3-ethyl-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide 178678-31-4P, trans-3-Butyl-3-ethyl-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide 178678-32-5P, 3-Butyl-3-ethyl-4-hydroxy-5-cyclohexylidene-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide 178678-35-8P 178678-38-1P
178678-39-2P 178678-41-6P 178678-44-9P 178678-47-2P 178678-48-3P
178678-52-9P 178678-53-0P 178678-54-1P 178897-95-5P 178897-96-6P
178897-99-9P 178898-02-7P 178898-03-8P 178898-04-9P 197372-66-0P
197372-70-6P 197372-72-8P 197372-73-9P 197372-74-0P 197372-75-1P
197372-79-5P 197372-80-8P 197372-81-9P 197372-82-0P 197372-83-1P
197372-84-2P 197372-85-3P 197372-86-4P 197372-87-5P 197372-88-6P
197372-90-0P 197373-06-1P 197373-16-3P 197373-17-4P 197373-18-5P
197373-19-6P 197373-20-9P 197373-22-1P 197373-24-3P 197373-25-4P
197373-26-5P 197373-27-6P 197373-32-3P 197373-35-6P 197373-38-9P
197373-39-0P 197373-40-3P 197373-41-4P 197373-45-8P 197373-48-1P
197373-54-9P 197373-59-4P 197377-85-8P 197377-86-9P
197377-90-5P 197377-94-9P 197377-96-1P 197377-98-3P 197378-13-5P
228113-66-4P **280105-90-0P** 289037-54-3P 289037-55-4P
289037-59-8P 289037-60-1P 289037-61-2P 289037-62-3P 289037-64-5P
289037-65-6P 289037-67-8P 289037-68-9P 289037-70-3P 289037-72-5P
289037-74-7P 289037-75-8P 289037-76-9P 289037-77-0P 289037-78-1P
289037-79-2P 289037-80-5P 289037-81-6P 289037-82-7P 289037-83-8P
289037-84-9P 289037-85-0P 289037-86-1P 289037-87-2P 289037-88-3P
289037-90-7P 289037-91-8P 289037-92-9P 289037-93-0P 289037-94-1P
289037-97-4P 289037-99-6P 289038-50-2P 361374-26-7P
525589-59-7P 526199-85-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of precursors of mono- and di-fluorinated benzothiepine inhibitors of apical sodium co-dependent bile acid transport (ASBT) and taurocholate uptake for treating hyperlipidemic conditions)

IT **197373-50-5P 197373-51-6P 197373-52-7P**
289037-96-3P 289037-98-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of precursors of mono- and di-fluorinated benzothiepine inhibitors of apical sodium co-dependent bile acid transport (ASBT) and taurocholate uptake for treating hyperlipidemic conditions)

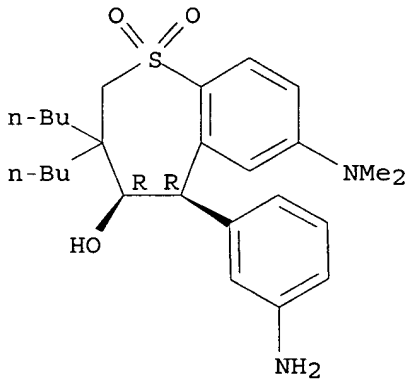
RN 197373-50-5 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



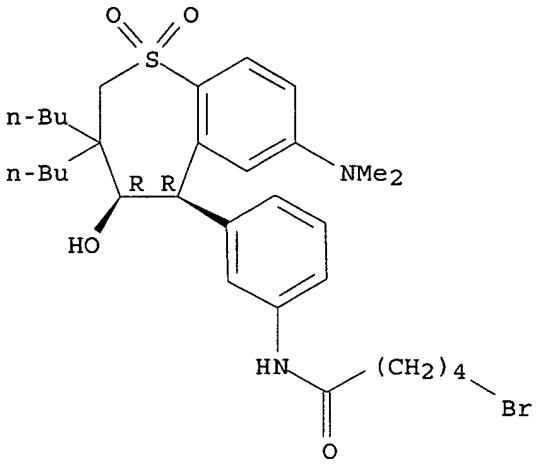
RN 197373-51-6 HCAPLUS
CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



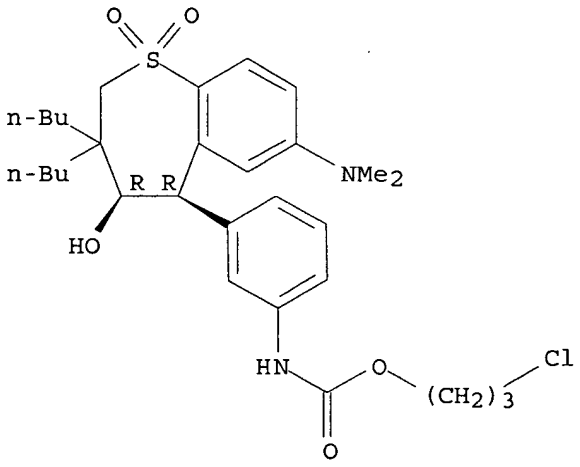
RN 197373-52-7 HCAPLUS
CN Pentanamide, 5-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



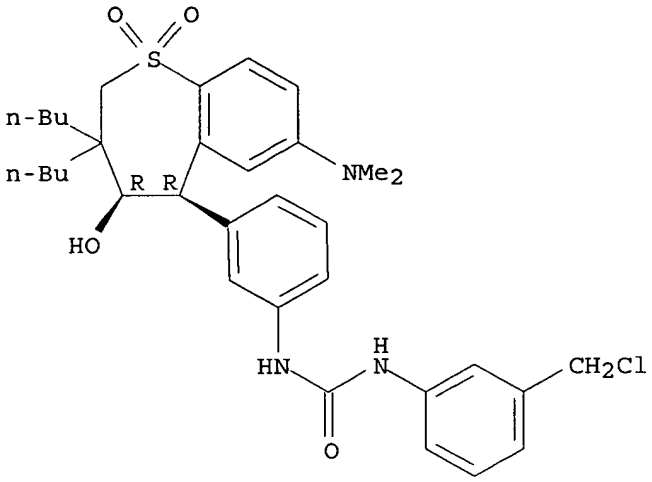
RN 289037-96-3 HCAPLUS
CN Carbamic acid, [3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, 3-chloropropyl ester, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 289037-98-5 HCAPLUS
CN Urea, N-[3-(chloromethyl)phenyl]-N'-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



IT **197373-54-9P 280105-90-0P 289037-97-4P**
289037-99-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of precursors of mono- and di-fluorinated benzothiepine inhibitors of apical sodium co-dependent bile acid transport (ASBT) and taurocholate uptake for treating hyperlipidemic conditions)

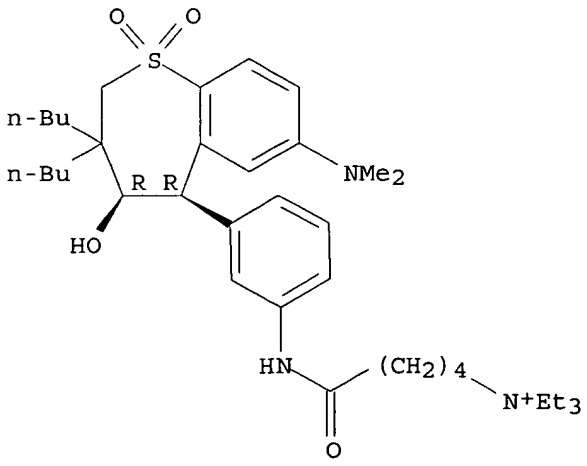
RN 197373-54-9 HCAPLUS

CN 1-Pentanaminium, 5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-oxo-, rel-, salt with trifluoroacetic acid (1:1) (9CI) (CA INDEX NAME)

CM 1

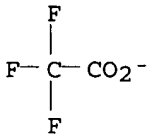
CRN 197373-53-8
CMF C37 H60 N3 O4 S

Relative stereochemistry.

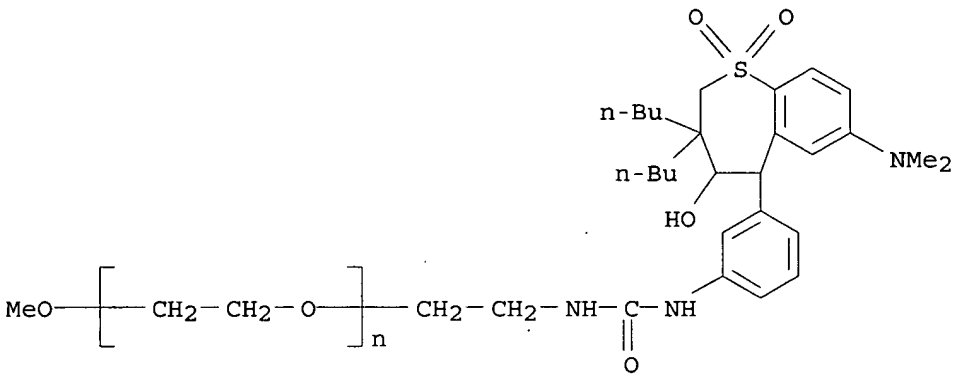


CM 2

CRN 14477-72-6
CMF C2 F3 O2

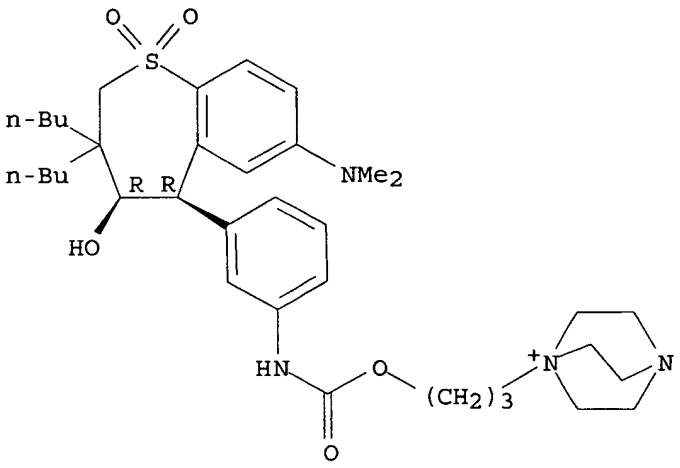


RN 280105-90-0 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-[2-[[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]carbonyl]amino]ethyl]-ω-methoxy-, rel- (9CI) (CA INDEX NAME)



RN 289037-97-4 HCAPLUS
CN 4-Aza-1-azoniabicyclo[2.2.2]octane, 1-[3-[[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]carbonyl]oxy]propyl]-, chloride, rel- (9CI) (CA INDEX NAME)

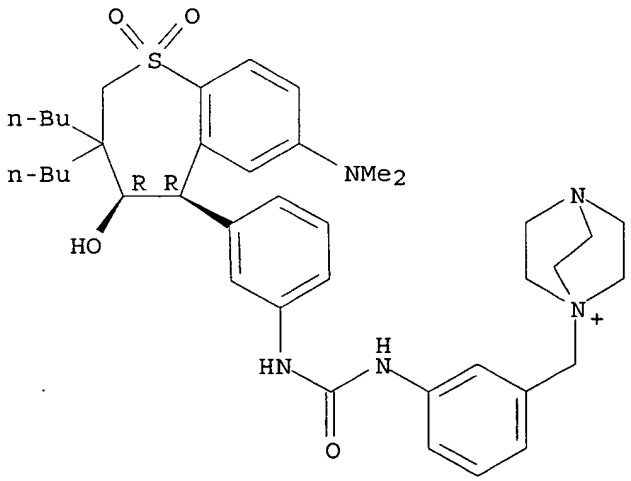
Relative stereochemistry.



● Cl⁻

RN 289037-99-6 HCAPLUS
CN 4-Aza-1-azoniabicyclo[2.2.2]octane, 1-[[3-[[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]carbonyl]amino]phenyl]methyl]-, chloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● Cl⁻

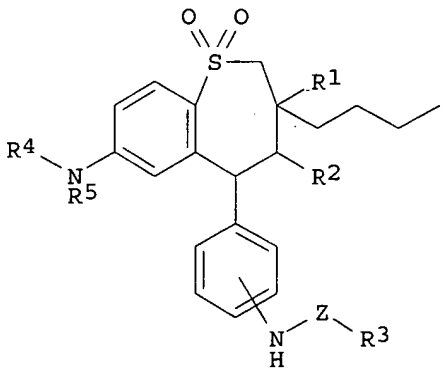
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:173440 HCAPLUS
DOCUMENT NUMBER: 138:215326
TITLE: Combined preparations, containing 1,4-benzothiepine-1,1-dioxide derivatives and other active substances for the treatment of hyperlipidemia
INVENTOR(S): Glombik, Heiner; Frick, Wendelin; Schaefer, Hans-Ludwig; Kramer, Werner
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003018024	A1	20030306	WO 2002-EP8908	20020809
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10140169	A1	20030306	DE 2001-10140169	20010822
DE 10142456	A1	20030320	DE 2001-10142456	20010831
CA 2457976	AA	20030306	CA 2002-2457976	20020809
EP 1425018	A1	20040609	EP 2002-796213	20020809
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002012031	A	20040803	BR 2002-12031	20020809
JP 2005501861	T2	20050120	JP 2003-522542	20020809
NZ 531293	A	20050826	NZ 2002-531293	20020809
NO 2004000702	A	20040519	NO 2004-702	20040218
PRIORITY APPLN. INFO.:			DE 2001-10140169 A	20010822
			DE 2001-10142456 A	20010831
			WO 2002-EP8908 W	20020809

OTHER SOURCE(S): MARPAT 138:215326
GI



I

AB The invention relates to mixts. of substances, containing 1,4-benzothiepine-1,1-dioxide derivs. of formula (I), in which the functional groups have the indicated meanings, their physiol. acceptable salts and physiol. functional derivs. as well as other active substances for the treatment of metabolic disorders especially hyperlipidemia. The combinations can also include antidiabetics, antiarthrytics etc. A typical capsule contains 100 mg of the drugs and 400 mg triglyceride mixture from coco fatty acids; other formulations are emulsions, tablets, dragees, and solns. Hamster that were fed with cholesterol-rich feed received orally the drug combination once daily for 10 days. Feces was analyzed for bile acids, blood lipid levels were measured and cholesterol was determined from liver.

IC ICM A61K031-55
ICS A61K031-395; A61P003-06

CC 1-10 (Pharmacology)
Section cross-reference(s): 63

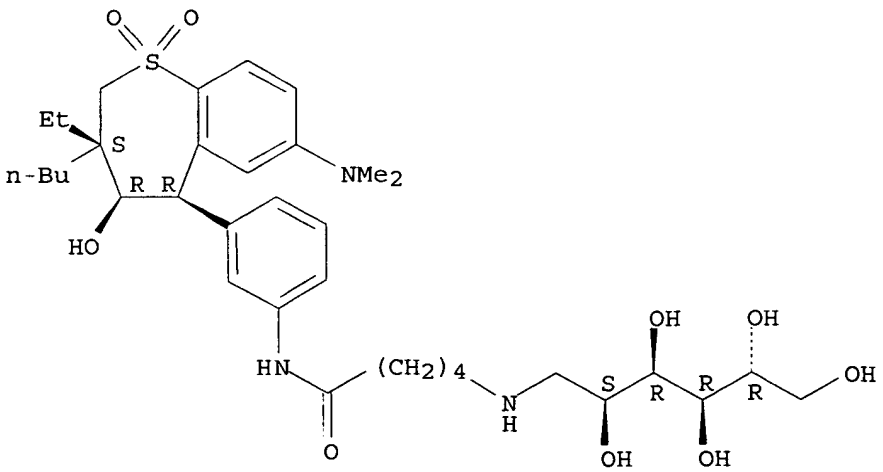
IT 56-03-1, Biguanide 300-62-9, Amphetamine 943-45-3, Fibric acid 2295-31-0, Glitazone 5395-30-2 9000-40-2, Carob gum 9002-72-6, Growth hormone 9004-10-8, Insulin, biological studies 9034-39-3, Growth hormone releasing hormone 11041-12-6, Cholestyramine 25614-03-3, Bromocriptine 25812-30-0, Gemfibrozil 49642-07-1, Statine 50925-79-6, Cholestipol 54870-28-9, Meglitinide 96829-58-2, Orlistat 99759-19-0, Tiqueside 129024-87-9, Doprexin 150332-35-7, Pamaqueside 163222-33-1, Ezetimibe **252047-40-8**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia)

IT **252047-40-8**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia)

RN 252047-40-8 HCAPLUS

CN D-Glucitol, 1-[[5-[[3-[(3S,4R,5R)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]amino]-1-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:487559 HCAPLUS
DOCUMENT NUMBER: 137:63115
TITLE: Preparation of diphenylazetidinone derivatives as hypolipidemic agents
INVENTOR(S): Glombik, Heiner; Kramer, Werner; Flohr, Stefanie; Frick, Wendelin; Heuer, Hubert; Jaehne, Gerhard; Lindenschmidt, Andreas; Schaefer, Hans-Ludwig
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002050068	A1	20020627	WO 2001-EP14532	20011211
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10064402	A1	20020627	DE 2000-10064402	20001221
DE 10154520	A1	20031002	DE 2001-10154520	20011107
CA 2431985	AA	20020627	CA 2001-2431985	20011211
AU 2002019173	A5	20020701	AU 2002-19173	20011211
EE 200300237	A	20030815	EE 2003-237	20011211
EP 1345932	A1	20030924	EP 2001-271371	20011211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001016482	A	20040203	BR 2001-16482	20011211
JP 2004516293	T2	20040603	JP 2002-551564	20011211
NZ 526592	A	20041126	NZ 2001-526592	20011211
RU 2275370	C2	20060427	RU 2003-122219	20011211
US 2002128252	A1	20020912	US 2001-21028	20011219
US 6498156	B2	20021224		
ZA 2003004092	A	20040419	ZA 2003-4092	20030527
ZA 2003004095	A	20040419	ZA 2003-4095	20030527
NO 2003002733	A	20030814	NO 2003-2733	20030616
HK 1059936	A1	20060127	HK 2004-102849	20040422
PRIORITY APPLN. INFO.:			DE 2000-10064402 A	20001221
			DE 2001-10154520 A	20011107
			WO 2001-EP14532 W	20011211

OTHER SOURCE(S): MARPAT 137:63115
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The compds. are suited for use e.g. as hypolipidemic drugs. The invention discloses preparation of diphenylazetidinone derivs. such as I [R1, R2, R3, R4, R5, R6 = C0-C30-alkylene-L {optionally containing O, CO, CH:CH, C.tplbond.C, N(alkyl), N(alkylphenyl), NH}, H, F, Cl, Br, I, CF3, NO2, CN, CO2H, CO2(alkyl), CONH2, CONH(alkyl), CON(alkyl)2, alkyl, alkenyl, alkynyl, O-alkyl, SO2NH2, SO2NH(alkyl) SO2N(alkyl)2, S-(alkyl), SO(alkyl), (un)substituted S(CH2)nPh, SO(CH2)nPh, SO2(alkyl), SO2(CH2)nPh, NH2, NH(alkyl), N(alkyl)2, NH(acyl), (un)substituted Ph, O(CH2)nPh; n = 0-6; L = II; R7, R9, R10 = Me, Et, Pr, butyl; R8 = H, OH, NH2, NH(alkyl)], and their physiol. acceptable salts, for their use as hypolipidemic agents. Thus, 1,2-diphenylazetidinone derivative III·trifluoroacetate (IV) was prepared via a multistep synthetic sequence starting from 7-[3-(3-butyl-7-dimethylamino-3-ethyl-4-hydroxy-1,1-dioxo-2,3,4,5-tetrahydro-1H-benzo[b]thiepin-5-yl)-phenylcarbamoyl]-heptanoic acid and 4-(4-aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxyphenyl]-azetidin-2-one. Azetidinone IV was tested for its cholesterol lowering ability [ED50 = 0.01 mg/mouse].

IC ICM C07D409-12
ICS A61K031-397; A61P009-00

CC 26-5 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 1, 63

IT **439113-82-3P 439113-89-0P 439113-91-4P**
439113-92-5P 439113-93-6P 439113-96-9P
439113-98-1P 439114-01-9P 439114-03-1P
439114-06-4P 439114-08-6P 439114-11-1P
439114-16-6P 439114-20-2P 439114-22-4P
439114-23-5P 439114-26-8P 439114-29-1P
439114-36-0P 439114-38-2P 439114-39-3P
439114-40-6P 439120-25-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of diphenylazetidinone derivs. as hypolipidemics)

IT 76-05-1, Trifluoroacetic acid, reactions 112-60-7, Tetraethylene glycol 124-04-9, Hexanedioic acid, reactions 1117-97-1, O,N-Dimethylhydroxylamine 1501-05-9 1663-39-4, tert-Butyl acrylate 7480-32-2, 4-Phenyl-oxazolidin-2-one 20256-89-7 23243-68-7 402820-38-6 439080-96-3 **439114-09-7** 439114-17-7 439114-41-7 **439114-42-8 439114-43-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of diphenylazetidinone derivs. as hypolipidemics)

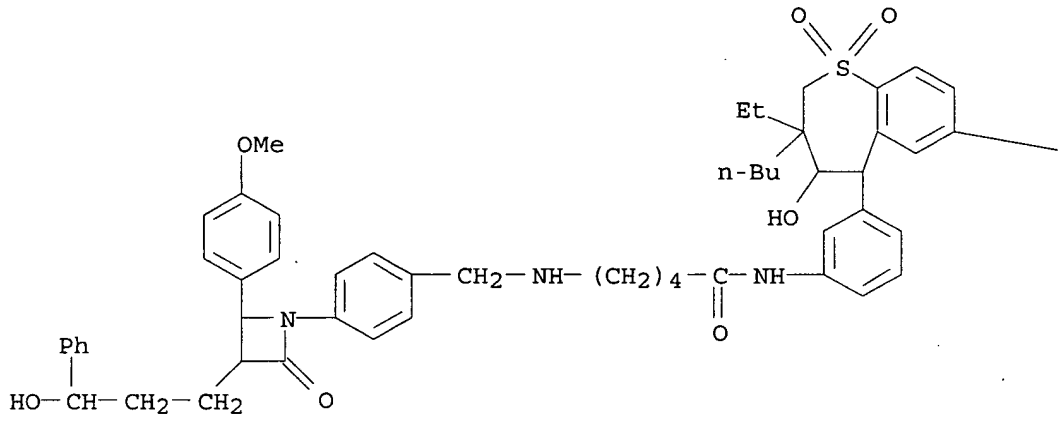
IT 94376-75-7P 439080-20-3P 439080-21-4P 439080-24-7P 439080-59-8P 439080-60-1P 439080-61-2P 439080-62-3P 439113-83-4P 439113-84-5P 439113-85-6P 439113-86-7P 439113-87-8P **439113-88-9P** 439113-90-3P **439113-94-7P 439113-99-2P** **439114-04-2P** 439114-12-2P 439114-13-3P **439114-14-4P** **439114-18-8P 439114-24-6P 439114-27-9P** 439114-30-4P 439114-31-5P **439114-32-6P 439114-34-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of diphenylazetidinone derivs. as hypolipidemics)

IT **439113-82-3P 439113-89-0P 439113-91-4P**
439113-92-5P 439113-93-6P 439113-96-9P
439113-98-1P 439114-01-9P 439114-03-1P
439114-06-4P 439114-08-6P 439114-11-1P
439114-16-6P 439114-20-2P 439114-22-4P
439114-23-5P 439114-26-8P 439114-29-1P
439114-36-0P 439114-38-2P 439114-39-3P

439114-40-6P 439120-25-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of diphenylazetidinone derivs. as hypolipidemics)

RN 439113-82-3 HCAPLUS
CN Pentanamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-5-[[[4-[3-(3-hydroxy-3-phenylpropyl)-2-(4-methoxyphenyl)-4-oxo-1-azetidinyl]phenyl]methyl]amino]- (9CI) (CA INDEX NAME)

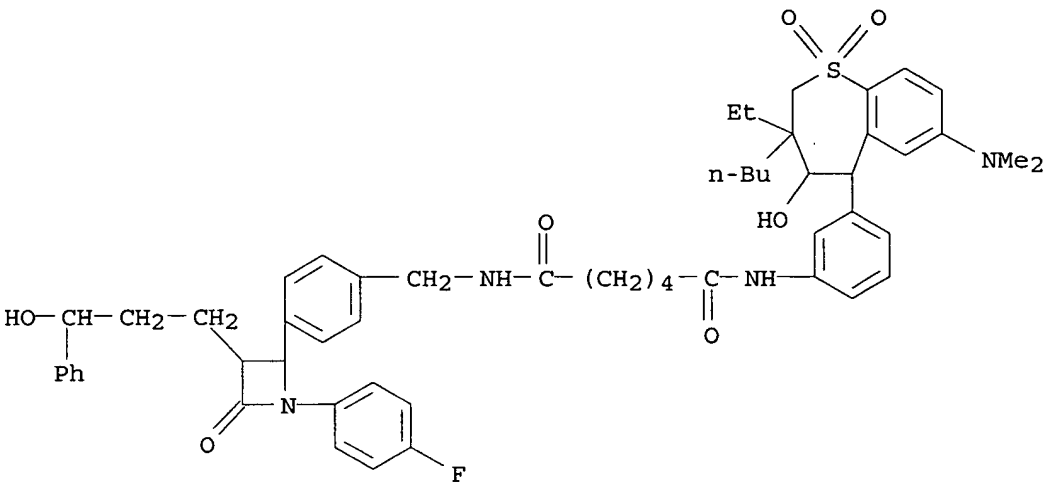
PAGE 1-A



PAGE 1-B

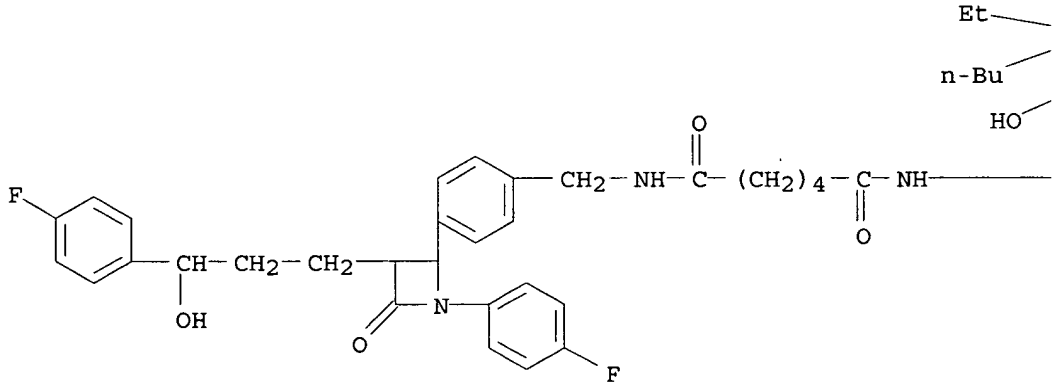
—NMe2

RN 439113-89-0 HCAPLUS
CN Hexanediamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N'-[[4-[1-(4-fluorophenyl)-3-(3-hydroxy-3-phenylpropyl)-4-oxo-2-azetidinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

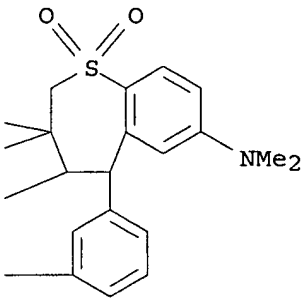


RN 439113-91-4 HCAPLUS
CN Hexanediamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N'-[[4-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

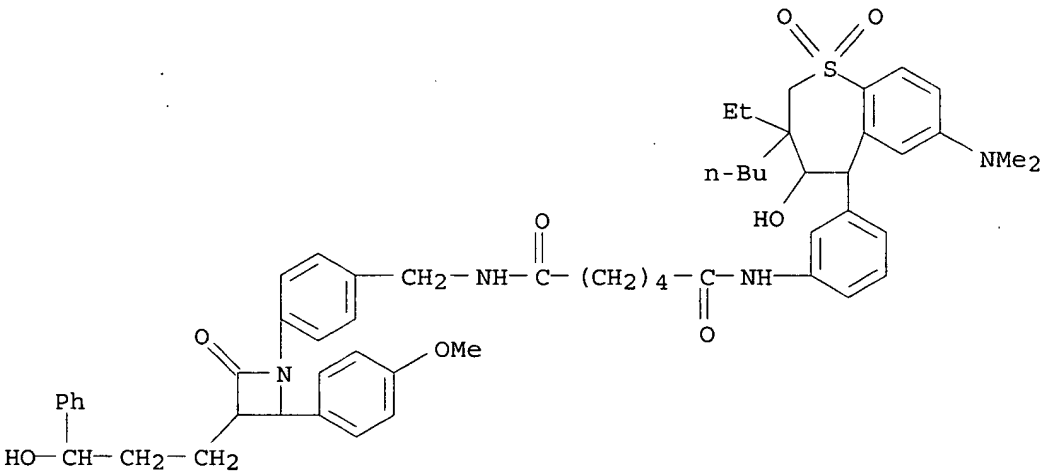
PAGE 1-A



PAGE 1-B

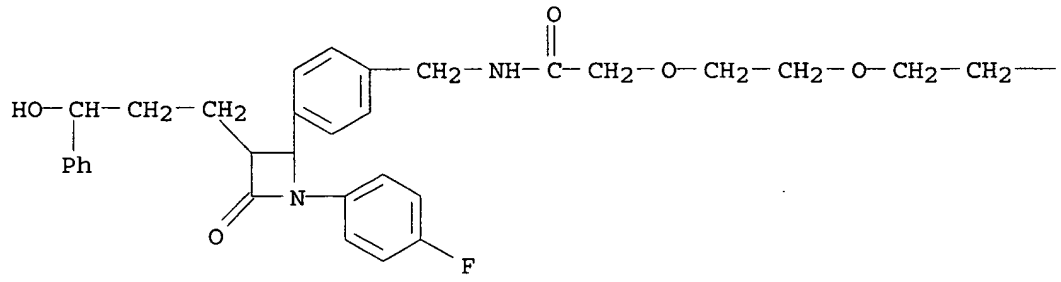


RN 439113-92-5 HCAPLUS
CN Hexanediamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N'-[[4-[3-(3-hydroxy-3-phenylpropyl)-2-(4-methoxyphenyl)-4-oxo-1-azetidinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

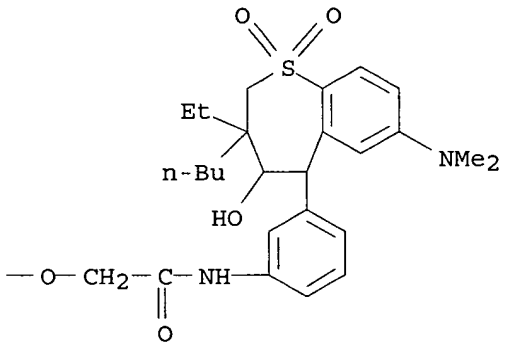


RN 439113-93-6 HCAPLUS
CN 5,8,11-Trioxa-2-azatridecan-13-amide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-1-[4-[1-(4-fluorophenyl)-3-(3-hydroxy-3-phenylpropyl)-4-oxo-2-azetidinyl]phenyl]-3-oxo- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B

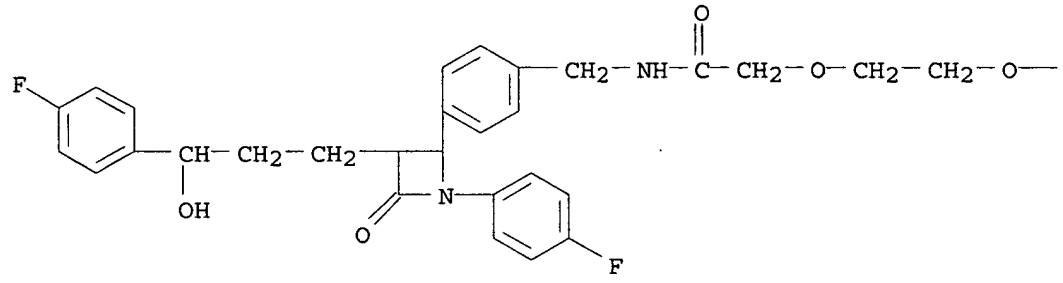


RN 439113-96-9 HCAPLUS
CN Acetamide, 2-[2-[2-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-2-oxoethoxy]ethoxy]-N-[[4-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

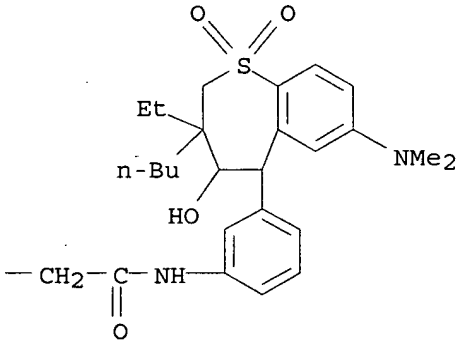
CM 1

CRN 439113-95-8
CMF C55 H64 F2 N4 O9 S

PAGE 1-A

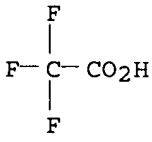


PAGE 1-B



CM 2

CRN 76-05-1
CMF C2 H F3 O2



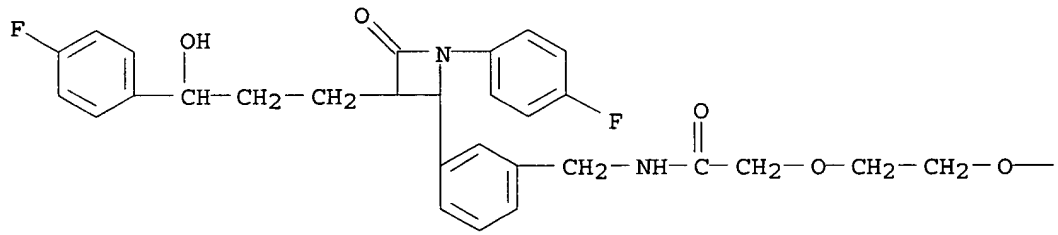
RN 439113-98-1 HCAPLUS
CN Acetamide, 2-[2-[2-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-2-oxoethoxy]ethoxy]-N-[[3-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]-, mono(trifluoroacetate)

(salt) (9CI) (CA INDEX NAME)

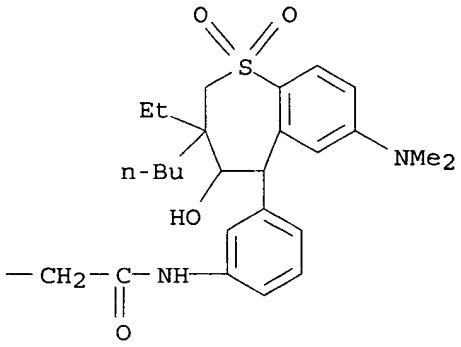
CM 1

CRN 439113-97-0
CMF C55 H64 F2 N4 O9 S

PAGE 1-A

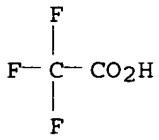


PAGE 1-B



CM 2

CRN 76-05-1
CMF C2 H F3 O2



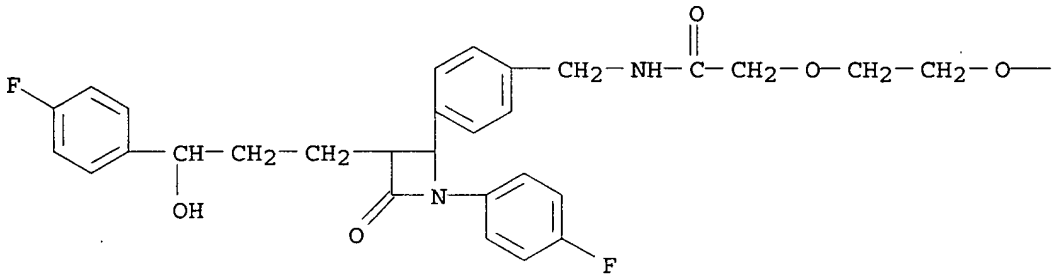
RN 439114-01-9 HCAPLUS
CN 5,8,11-Trioxa-2-azatridecan-13-amide, N-[3-[3-butyl-7-(dimethylamino)-3-

ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-1-[4-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]-3-oxo-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

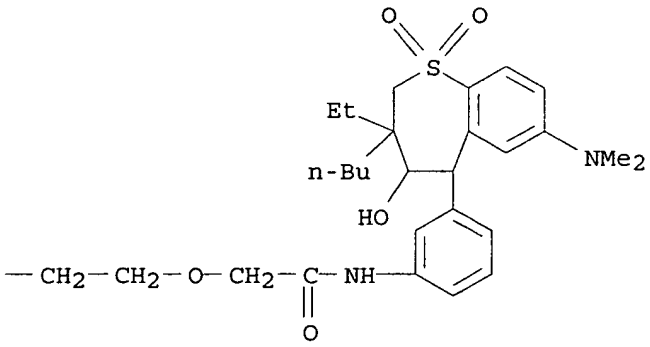
CM 1

CRN 439114-00-8
CMF C57 H68 F2 N4 O10 S

PAGE 1-A

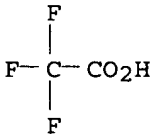


PAGE 1-B



CM 2

CRN 76-05-1
CMF C2 H F3 O2

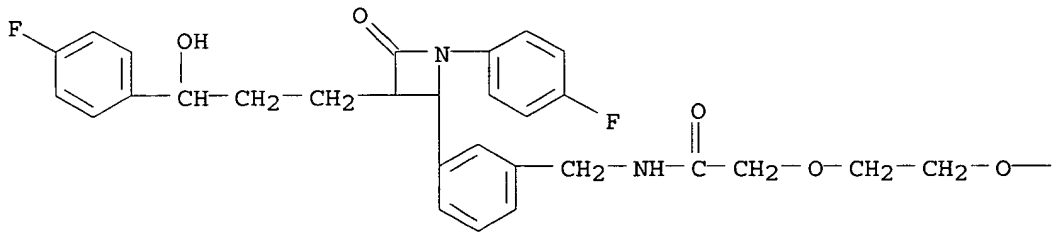


RN 439114-03-1 HCAPLUS
CN 5,8,11-Trioxa-2-azatridecan-13-amide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-1-[3-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]-3-oxo-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

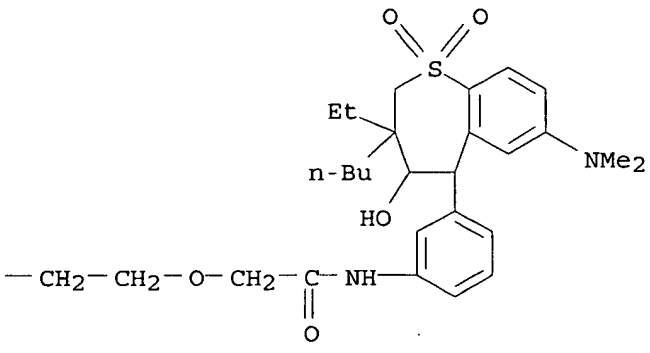
CM 1

CRN 439114-02-0
CMF C57 H68 F2 N4 O10 S

PAGE 1-A



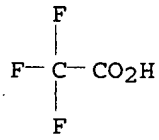
PAGE 1-B



CM 2

CRN 76-05-1

CMF C2 H F3 O2

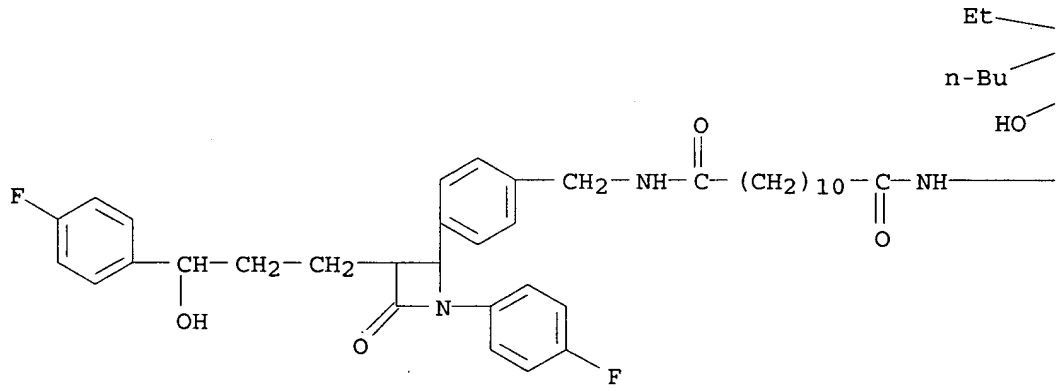


RN 439114-06-4 HCAPLUS
CN Dodecanediamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N'-[[4-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

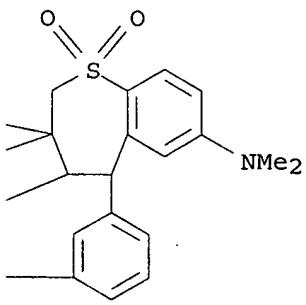
CM 1

CRN 439114-05-3
CMF C61 H76 F2 N4 O7 S

PAGE 1-A

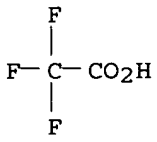


PAGE 1-B



CM 2

CRN 76-05-1
CMF C2 H F3 O2

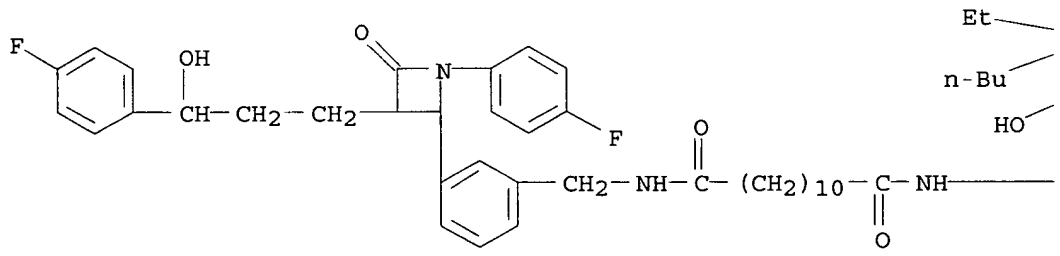


RN 439114-08-6 HCAPLUS
CN Dodecanediamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N'-[[3-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

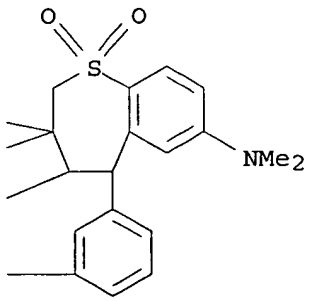
CM 1

CRN 439114-07-5
CMF C61 H76 F2 N4 O7 S

PAGE 1-A

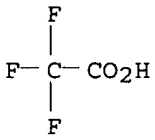


PAGE 1-B



CM 2

CRN 76-05-1
CMF C2 H F3 O2

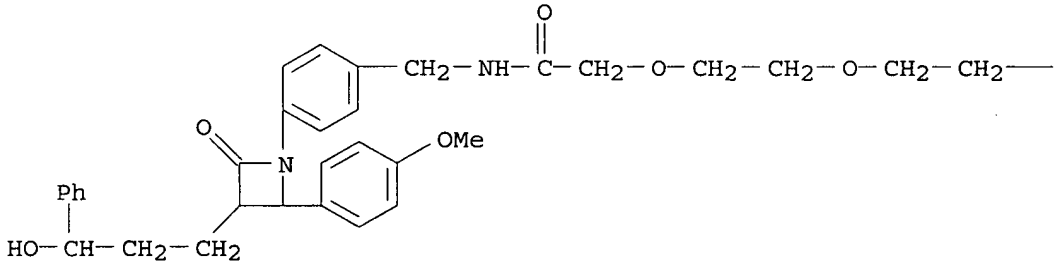


RN 439114-11-1 HCAPLUS
CN 5,8,11-Trioxa-2-azatridecan-13-amide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-1-[4-[3-(3-hydroxy-3-phenylpropyl)-2-(4-methoxyphenyl)-4-oxo-1-azetidinyl]phenyl]-3-oxo-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

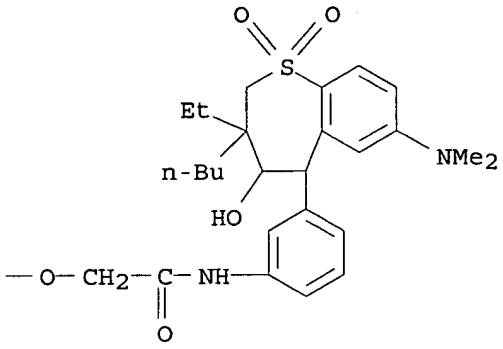
CM 1

CRN 439114-10-0
CMF C58 H72 N4 O11 S

PAGE 1-A

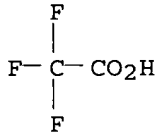


PAGE 1-B



CM 2

CRN 76-05-1
CMF C2 H F3 O2

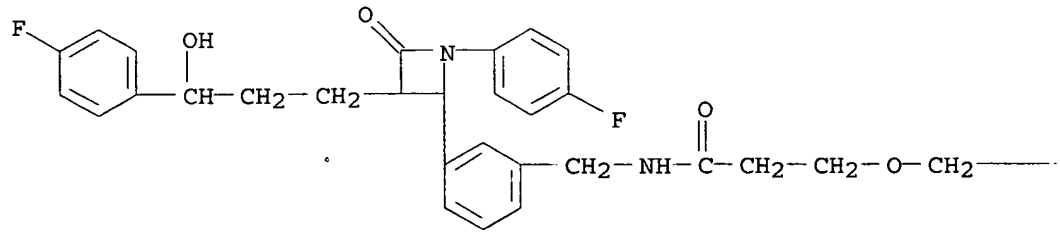


RN 439114-16-6 HCAPLUS
CN 4,7,10,13,16-Pentaoxanonadecanediamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N'-[[3-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

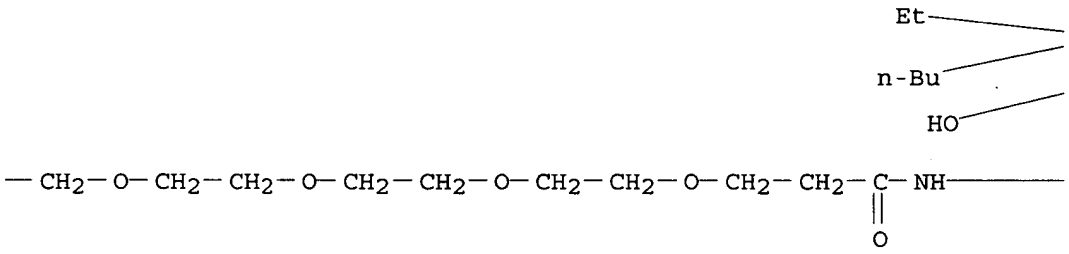
CM 1

CRN 439114-15-5
CMF C63 H80 F2 N4 O12 S

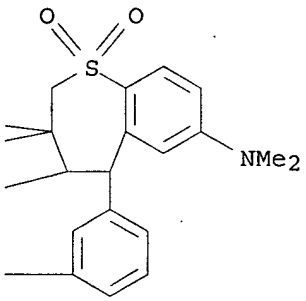
PAGE 1-A



PAGE 1-B

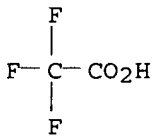


PAGE 1-C



CM 2

CRN 76-05-1
CMF C2 H F3 O2

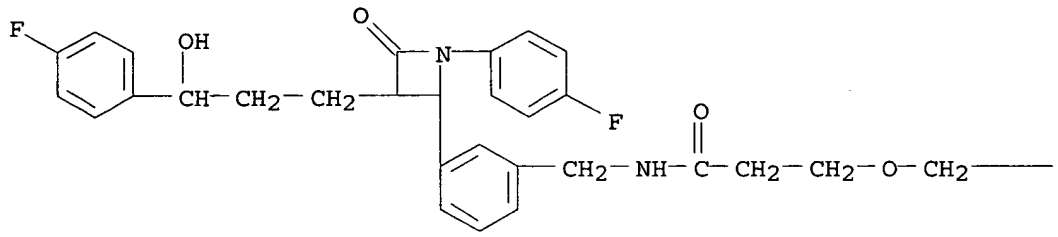


RN 439114-20-2 HCAPLUS
CN 4,7,10,13,16,19,22-Heptaoxapentacosanediamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N'-[[3-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

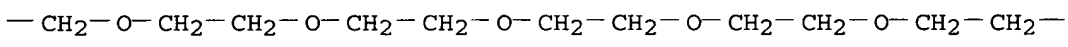
CM 1

CRN 439114-19-9
CMF C67 H88 F2 N4 O14 S

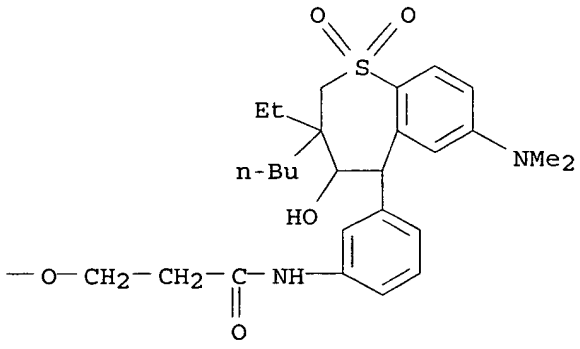
PAGE 1-A



PAGE 1-B

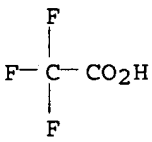


PAGE 1-C



CM 2

CRN 76-05-1
CMF C2 H F3 O2

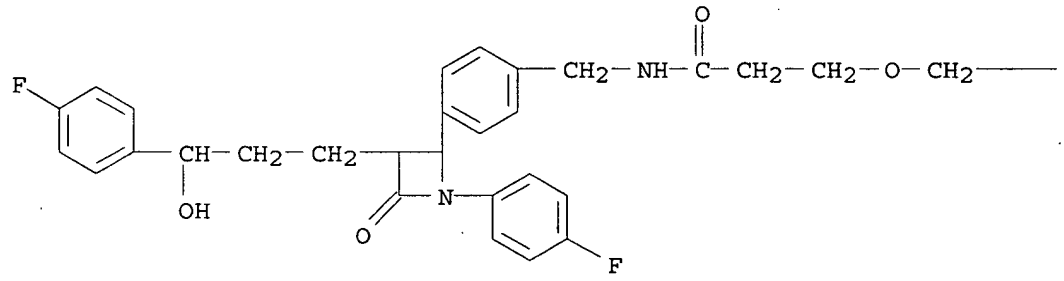


RN 439114-22-4 HCAPLUS
CN 4,7,10,13,16-Pentaoxanonadecanediamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N'-[[4-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

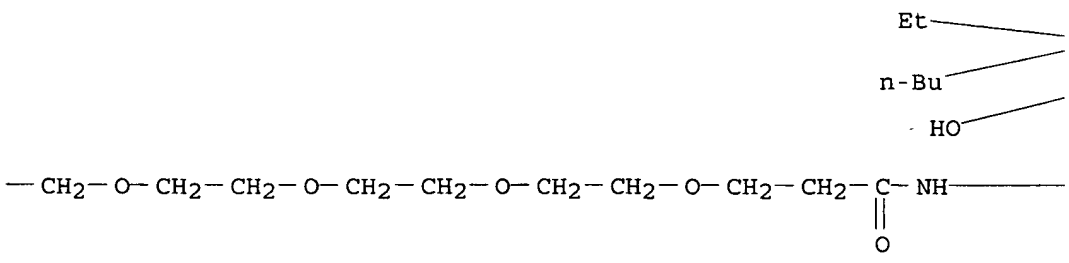
CM 1

CRN 439114-21-3
CMF C63 H80 F2 N4 O12 S

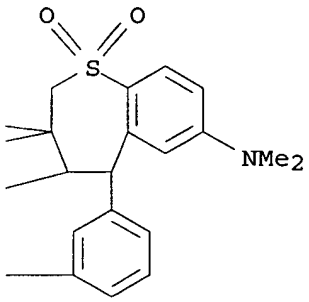
PAGE 1-A



PAGE 1-B

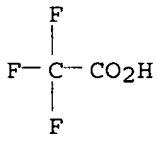


PAGE 1-C

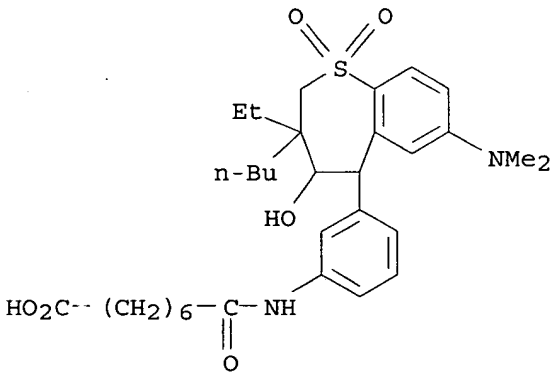


CM 2

CRN 76-05-1
CMF C2 H F3 O2



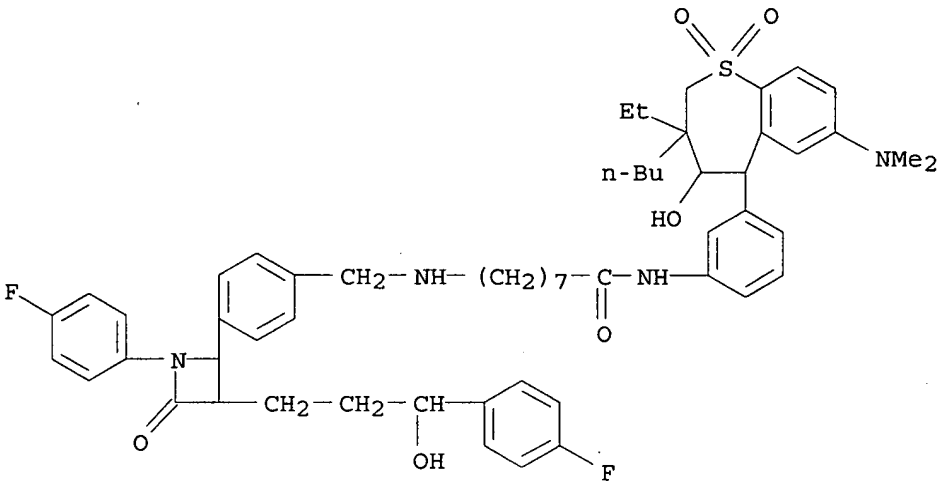
RN 439114-23-5 HCAPLUS
CN Octanoic acid, 8-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-8-oxo- (9CI) (CA INDEX NAME)



RN 439114-26-8 HCAPLUS
CN Octanamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-8-[[[4-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]amino]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

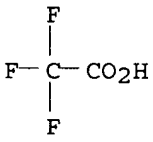
CM 1

CRN 439114-25-7
CMF C57 H70 F2 N4 O6 S



CM 2

CRN 76-05-1
CMF C2 H F3 O2

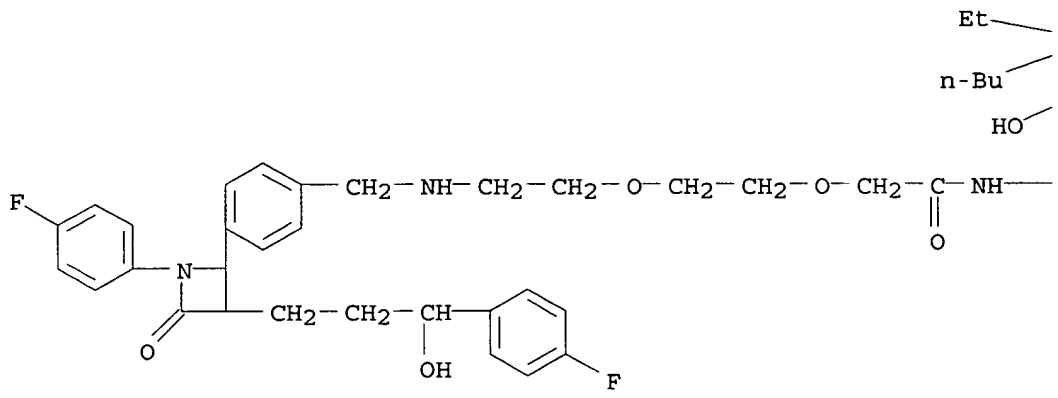


RN 439114-29-1 HCAPLUS
CN Acetamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-2-[2-[2-[[[4-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]amino]ethoxy]ethoxy]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

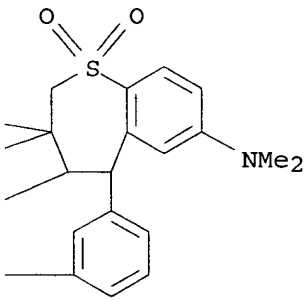
CM 1

CRN 439114-28-0
CMF C55 H66 F2 N4 O8 S

PAGE 1-A

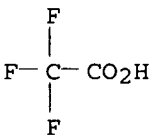


PAGE 1-B



CM 2

CRN 76-05-1
CMF C2 H F3 O2

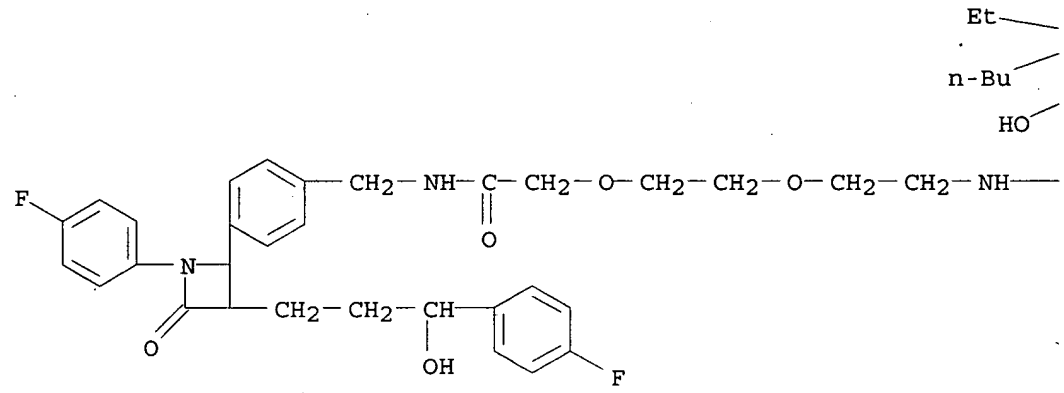


RN 439114-36-0 HCAPLUS
CN Acetamide, 2-[2-[2-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]ethoxy]ethoxy]-N-[[4-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

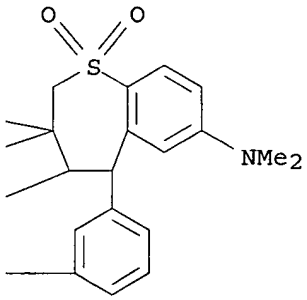
CM 1

CRN 439114-35-9
CMF C55 H66 F2 N4 O8 S

PAGE 1-A

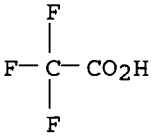


PAGE 1-B



CM 2

CRN 76-05-1
CMF C2 H F3 O2



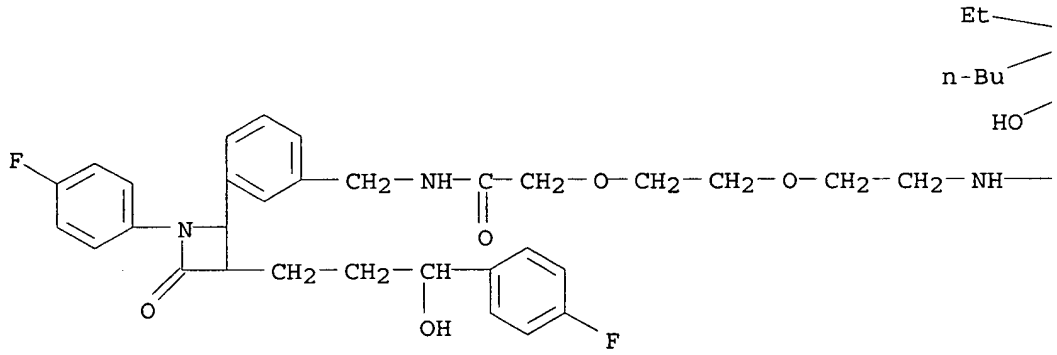
RN 439114-38-2 HCAPLUS

CN Acetamide, 2-[2-[2-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]ethoxy]ethoxy]-N-[[3-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

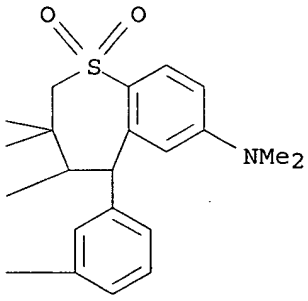
CM 1

CRN 439114-37-1
CMF C55 H66 F2 N4 O8 S

PAGE 1-A

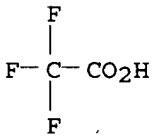


PAGE 1-B



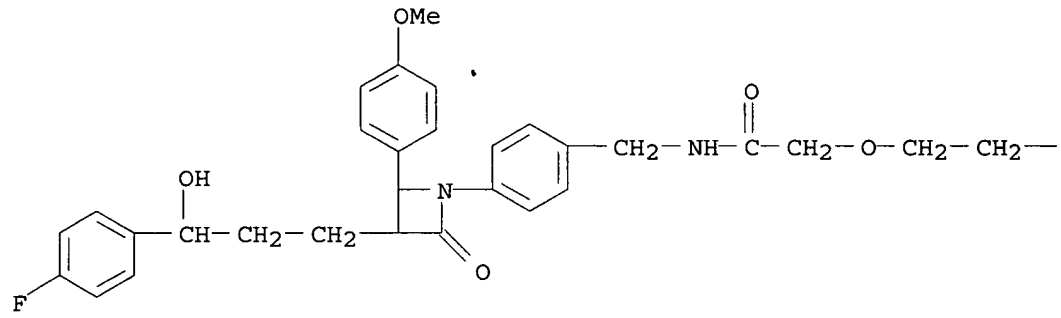
CM 2

CRN 76-05-1
CMF C2 H F3 O2

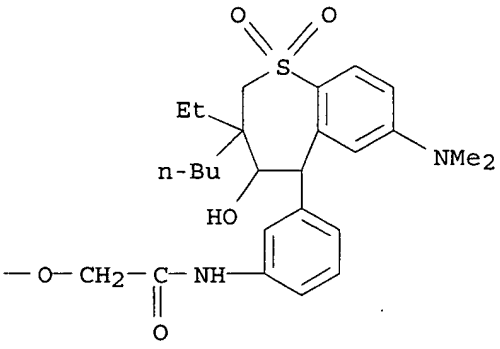


RN 439114-39-3 HCAPLUS
CN Acetamide, 2-[2-[2-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-2-oxoethoxy]ethoxy]-N-[[4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxo-1-azetidinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

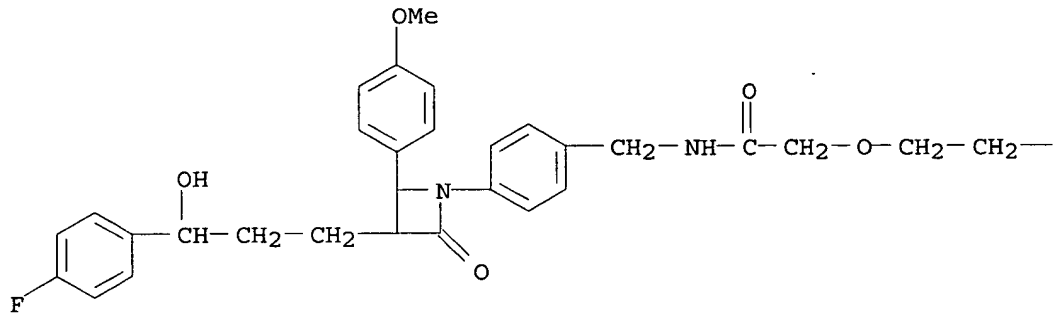


PAGE 1-B

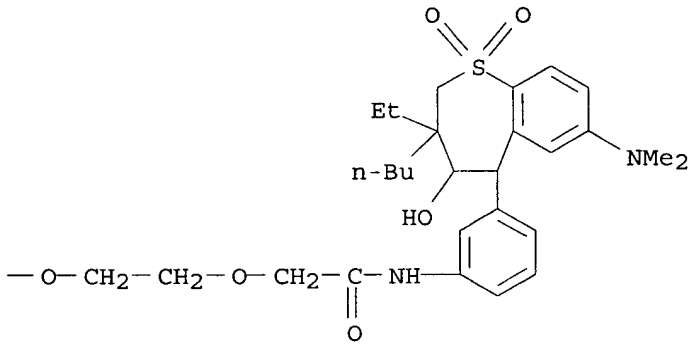


RN 439114-40-6 HCAPLUS
CN 5,8,11-Trioxa-2-azatridecan-13-amide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-1-[4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxo-1-azetidinyl]phenyl]-3-oxo- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B

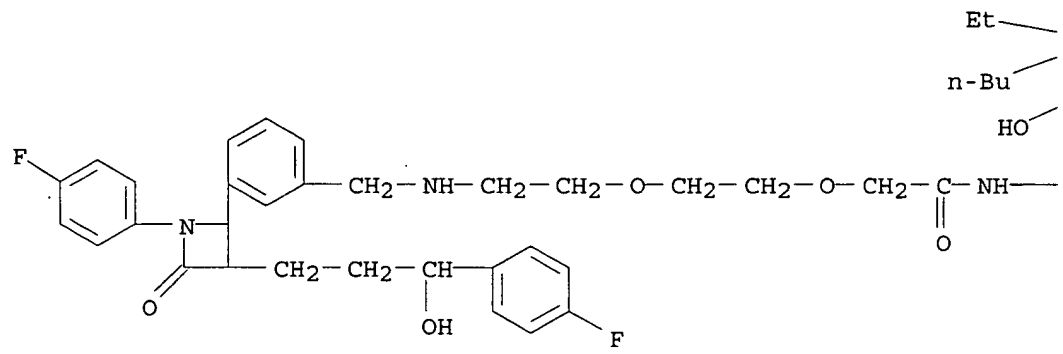


RN 439120-25-9 HCAPLUS
CN Acetamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-2-[2-[2-[[[3-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]amino]ethoxy]ethoxy]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

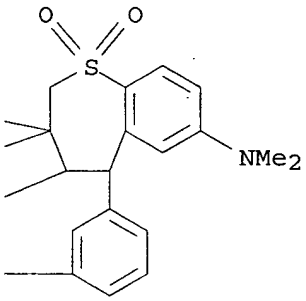
CM 1

CRN 439120-24-8
CMF C55 H66 F2 N4 O8 S

PAGE 1-A

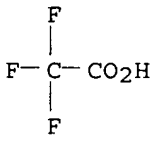


PAGE 1-B

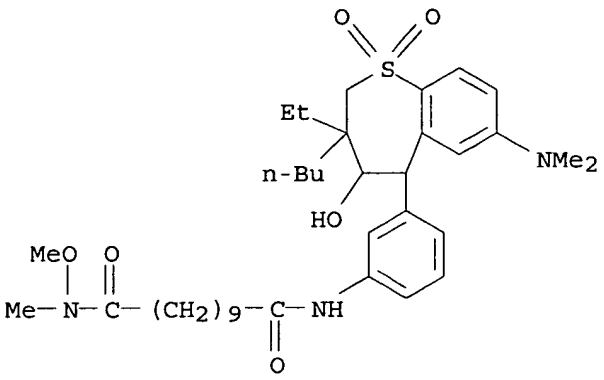


CM 2

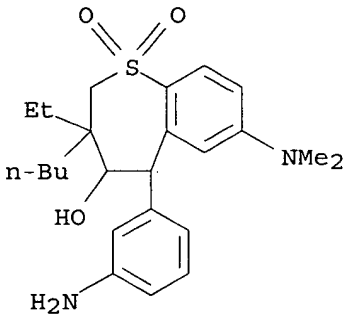
CRN 76-05-1
CMF C2 H F3 O2



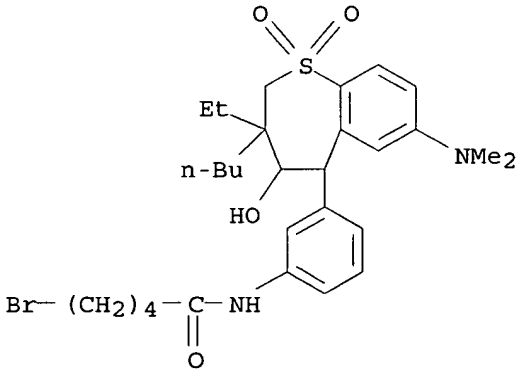
IT **439114-09-7 439114-42-8 439114-43-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of diphenylazetidinone derivs. as hypolipidemics)
RN 439114-09-7 HCAPLUS
CN Undecanediamide, N'-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N-methoxy-N-methyl- (9CI) (CA INDEX NAME)



RN 439114-42-8 HCAPLUS
CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-, 1,1-dioxide (9CI) (CA INDEX NAME)



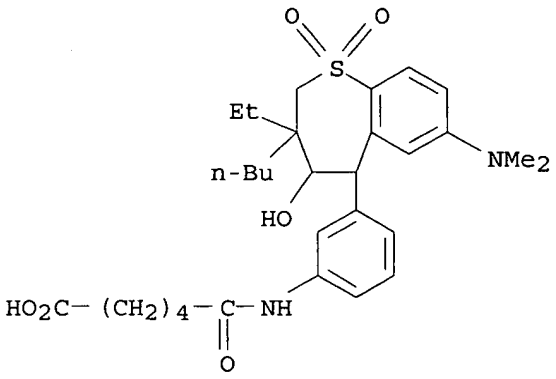
RN 439114-43-9 HCAPLUS
CN Pentanamide, 5-bromo-N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]- (9CI) (CA INDEX NAME)



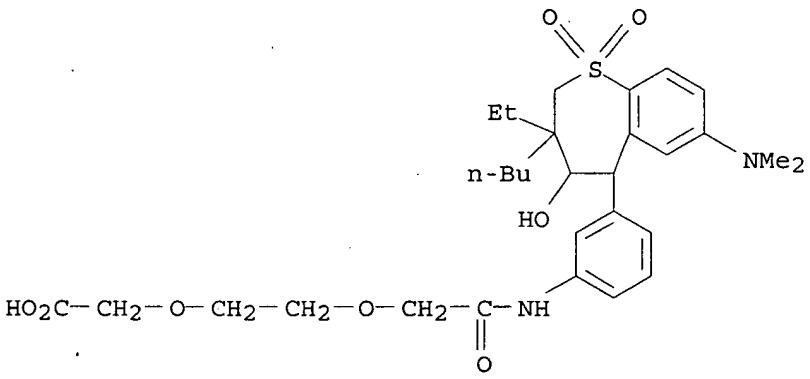
IT **439113-88-9P 439113-94-7P 439113-99-2P**
439114-04-2P 439114-14-4P 439114-18-8P
439114-24-6P 439114-27-9P 439114-32-6P
439114-34-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)
(preparation of diphenylazetidinone derivs. as hypolipidemics)

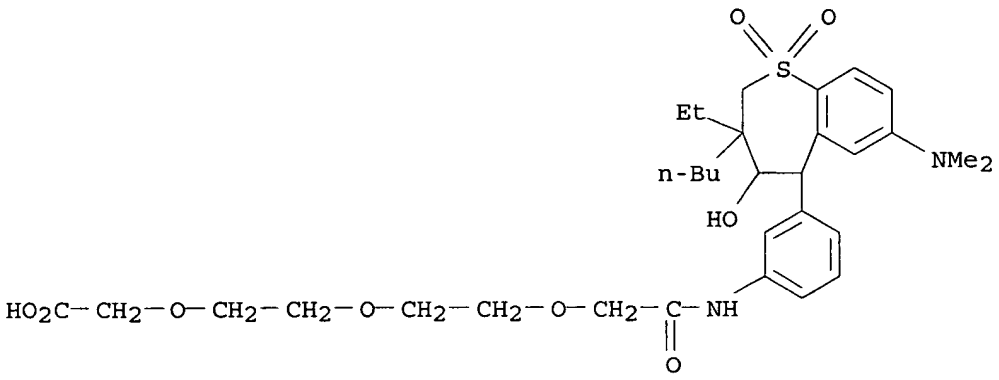
RN 439113-88-9 HCAPLUS
CN Hexanoic acid, 6-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-6-oxo- (9CI) (CA INDEX NAME)



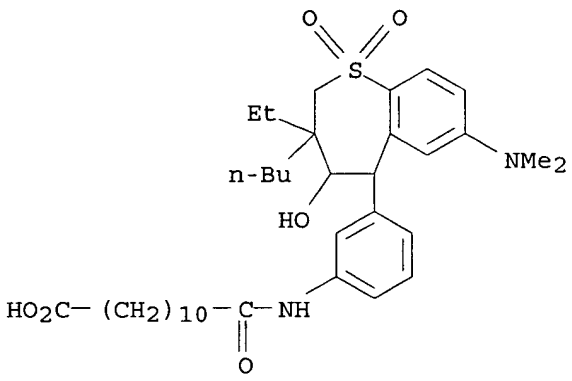
RN 439113-94-7 HCAPLUS
CN Acetic acid, [2-[2-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-2-oxoethoxy]ethoxy]- (9CI) (CA INDEX NAME)



RN 439113-99-2 HCAPLUS
CN Acetic acid, [2-[2-[2-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-2-oxoethoxy]ethoxy]ethoxy]- (9CI) (CA INDEX NAME)

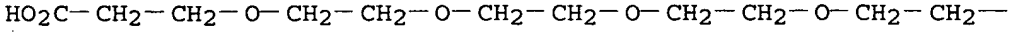


RN 439114-04-2 HCAPLUS
CN Dodecanoic acid, 12-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-12-oxo- (9CI) (CA INDEX NAME)

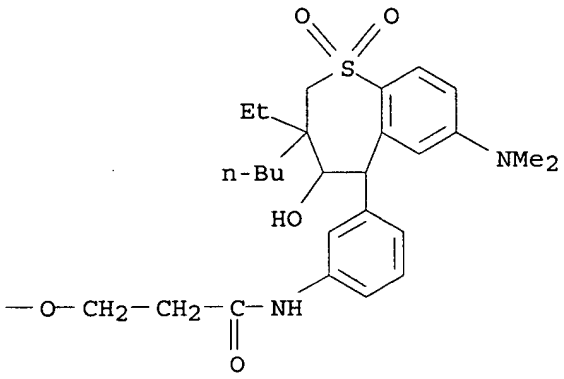


RN 439114-14-4 HCAPLUS
CN 4,7,10,13,16-Pentaoxanonadecanoic acid, 19-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-19-oxo- (9CI) (CA INDEX NAME)

PAGE 1-A

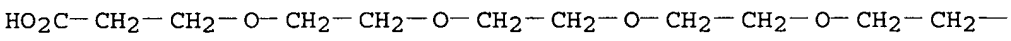


PAGE 1-B

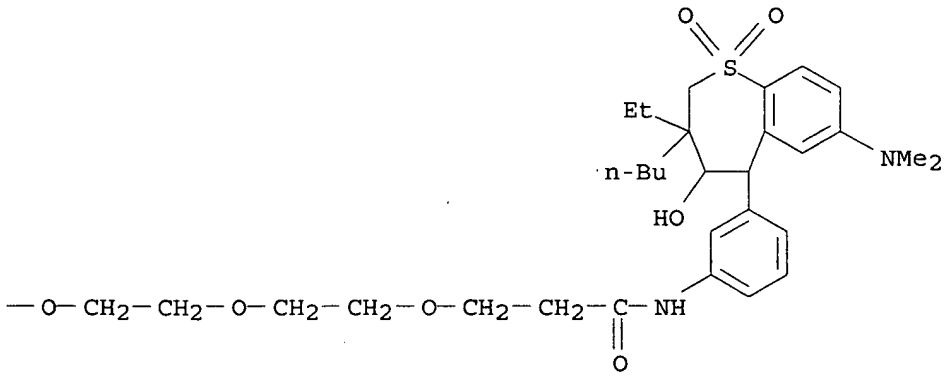


RN 439114-18-8 HCAPLUS
CN 4,7,10,13,16,19,22-Heptaoxapentacosanoic acid, 25-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-25-oxo- (9CI) (CA INDEX NAME)

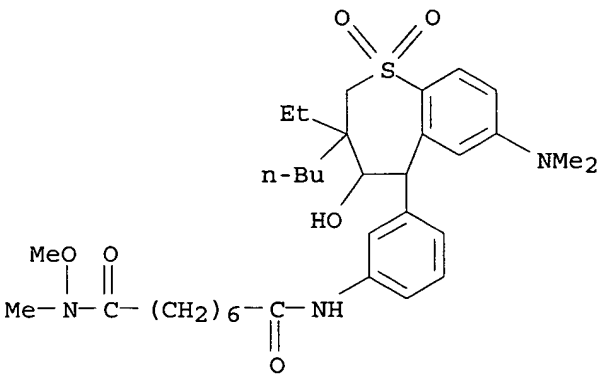
PAGE 1-A



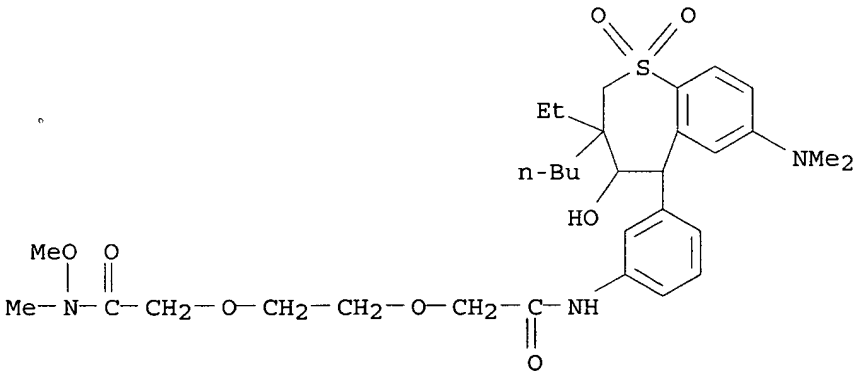
PAGE 1-B



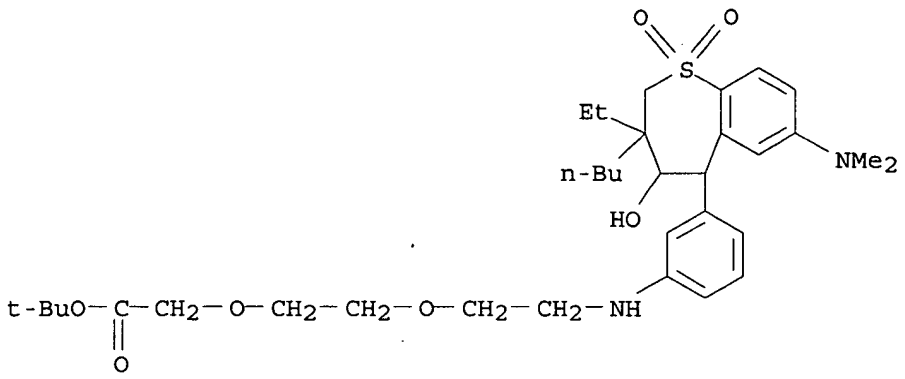
RN 439114-24-6 HCAPLUS
CN Octanediamide, N'-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N-methoxy-N-methyl- (9CI) (CA INDEX NAME)



RN 439114-27-9 HCAPLUS
CN 2,6,9-Trioxa-3-azaundecan-11-amide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-3-methyl-4-oxo- (9CI) (CA INDEX NAME)



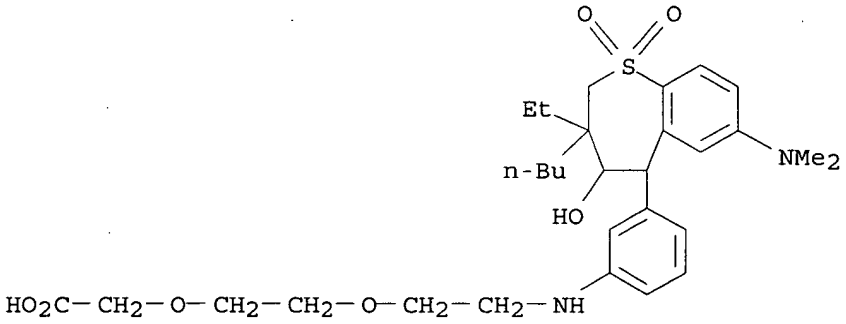
RN 439114-32-6 HCAPLUS
CN Acetic acid, [2-[2-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]ethoxy]ethoxy]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 439114-34-8 HCAPLUS
CN Acetic acid, [2-[2-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]ethoxy]ethoxy]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

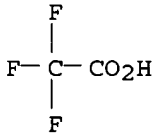
CM 1

CRN 439114-33-7
CMF C30 H44 N2 O7 S



CM 2

CRN 76-05-1
CMF C2 H F3 O2



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:693092 HCAPLUS
DOCUMENT NUMBER: 135:257253
TITLE: Preparation of tetrahydrobenzothiepines and naphthalenes useful in combination therapy with HMG Co-A reductase inhibitors for the prophylaxis and treatment of hyperlipidemic conditions and disorders.
INVENTOR(S): Keller, Bradley T.; Tremont, Samuel J.; Glenn, Kevin C.; Manning, Robert E.
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: PCT Int. Appl., 182 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2001068096	A2	20010920	WO 2001-US7505		20010308
WO 2001068096	A3	20020725			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
US 2002061888	A1	20020523	US 2001-802313		20010308
US 2003232834	A1	20031218	US 2002-204672		20021126
US 2004082647	A1	20040429	US 2003-419266		20030421
US 2004110761	A1	20040610	US 2003-611942		20030703
PRIORITY APPLN. INFO.:			US 2000-188361P	P	20000310
			US 2000-188378P	P	20000310
			US 2001-802279	A3	20010308
			US 2001-802313	B1	20010308
			WO 2001-US7505	W	20010308

AB A method for the treatment and/or prophylaxis of a hyperlipidemic condition or disorder comprises the administration of ≥1 HMG Co-A reductase inhibitors and one or more specific apical Na codependent bile acid transporter (ASBT) inhibitors is claimed. Thus, (4R,5R)-1-[[4-[4-[3-butyl-3-ethyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxo-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride (3,3-di-Bu analog preparation given) 0.375 mg/kg/day and lovastatin 0.45 mg/kg/day orally in dogs reduced serum triglycerides by 37% at 4 wk.

IC ICM A61K031-495
ICS A61K031-38; A61K031-235

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 25, 27, 63

IT 73573-88-3, Mevastatin 75330-75-5, Lovastatin 79902-63-9, Simvastatin 81093-37-0, Pravastatin 93957-54-1, Fluvastatin 134523-00-5, Atorvastatin 145599-86-6, Cerivastatin 147098-20-2, ZD-4522 147526-32-7 151165-96-7 280105-82-0 280105-83-1 280105-84-2 **280105-88-6 280105-89-7** 280105-91-1 280105-92-2 280757-38-2 289037-90-7 289039-91-4 361484-19-7 361484-23-3 361484-26-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of tetrahydrobenzothiepines and naphthalenes useful in combination therapy with HMG Co-A reductase inhibitors for the prophylaxis and treatment of hyperlipidemic conditions and disorders)

IT 16473-35-1P 24765-57-9P 25784-91-2P, 2-Chloro-5-nitrobenzoyl chloride
70132-87-5P 174747-95-6P 197373-49-2P **197373-50-5P**
197373-51-6P 197373-55-0P 197373-56-1P 197373-57-2P
197378-07-7P 197378-31-7P 197378-32-8P 197378-46-4P 197378-48-6P
197378-50-0P 197378-52-2P 197378-54-4P 197378-56-6P 197378-58-8P
228113-65-3P 361373-66-2P 361373-79-7P 361373-81-1P 361373-83-3P
361373-85-5P 361373-87-7P 361373-89-9P 361373-91-3P 361373-92-4P
361373-94-6P 361373-96-8P 361373-98-0P 361374-00-7P 361374-02-9P
361374-06-3P 361374-08-5P 361484-28-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of tetrahydrobenzothiepines and naphthalenes useful in combination therapy with HMG Co-A reductase inhibitors for the prophylaxis and treatment of hyperlipidemic conditions and disorders)

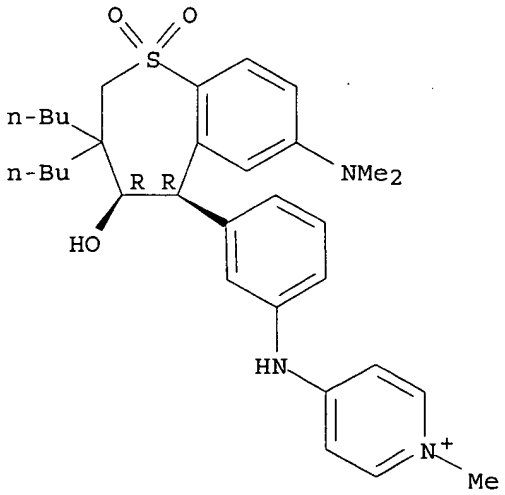
IT **280105-88-6 280105-89-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of tetrahydrobenzothiepines and naphthalenes useful in combination therapy with HMG Co-A reductase inhibitors for the prophylaxis and treatment of hyperlipidemic conditions and disorders)

RN 280105-88-6 HCAPLUS
CN Pyridinium, 4-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-1-methyl-, rel-, salt with 4-methylbenzenesulfonic acid (1:1) (9CI) (CA INDEX NAME)

CM 1

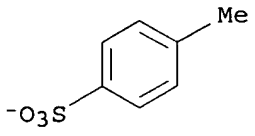
CRN 280105-87-5
CMF C32 H44 N3 O3 S

Relative stereochemistry.



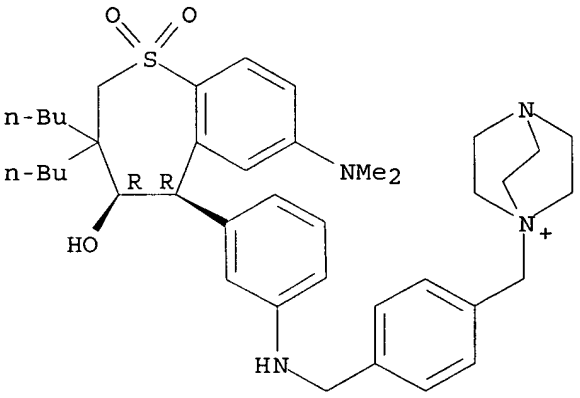
CM 2

CRN 16722-51-3
CMF C7 H7 O3 S



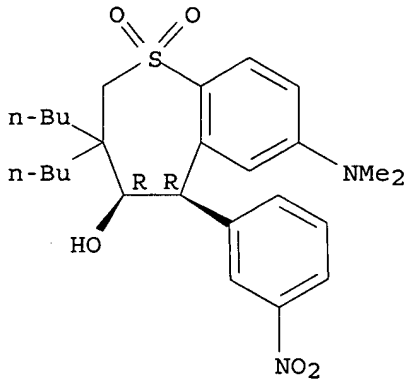
RN 280105-89-7 HCAPLUS
CN 4-Aza-1-azoniabicyclo[2.2.2]octane, 1-[[4-[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]methyl]phenyl]methyl]-, chloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



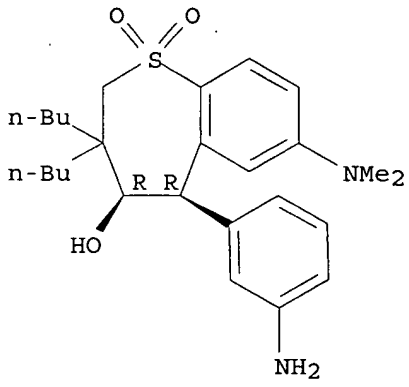
IT **197373-50-5P 197373-51-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of tetrahydrobenzothiepines and naphthalenes useful in combination therapy with HMG Co-A reductase inhibitors for the prophylaxis and treatment of hyperlipidemic conditions and disorders)
RN 197373-50-5 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 197373-51-6 HCAPLUS
CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L9 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:560070 HCAPLUS
DOCUMENT NUMBER: 135:137410
TITLE: Preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors.
INVENTOR(S): Keller, Bradley T.; Glenn, Kevin C.; Manning, Robert E.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA
SOURCE: U.S., 356 pp., Cont.-in-part of U.S. Ser. No. 831,284, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6268392	B1	20010731	US 1998-37308	19980309

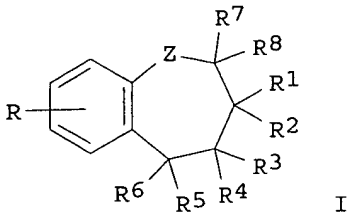
CA 2506703	AA	19970918	CA 1997-2506703	19970311
EP 1440972	A1	20040728	EP 2004-10088	19970311
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
AU 761249	B2	20030529	AU 2000-53394	20000816
US 6420417	B1	20020716	US 2000-676466	20000929
US 2003171426	A1	20030911	US 2002-76091	20020215
US 6642268	B2	20031104		
US 2004157915	A1	20040812	US 2003-620460	20030717
US 6943189	B2	20050913		

PRIORITY APPLN. INFO.:

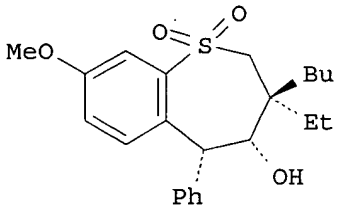
US 1994-305526	A2 19940912
US 1995-517051	A1 19950821
US 1996-13119P	P 19960311
US 1997-40660P	P 19970311
US 1997-816065	A2 19970311
US 1997-831284	B2 19970331
AU 1997-23266	A3 19970311
CA 1997-2248586	A3 19970311
EP 1997-915976	A3 19970311
US 1998-37308	A3 19980309
US 2000-676466	A3 20000929
US 2002-76091	A1 20020215

OTHER SOURCE(S): MARPAT 135:137410

GI



I



II

AB Title compds. [I; R = H or 1-4 of alkyl, alkenyl, alkynyl, acyloxy, aryl, aralkyl, halo, etc.; R1, R2 = H, (substituted) alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, alkoxy, dialkylamino, etc.; R1R2C = cycloalkylidene; R3, R4 = H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocyclyl, heteroaryl, etc.; R3R4 = O, S, NOR11, etc.; R11 = H, alkyl, alkenyl, alkynyl, aryl, aralkyl, etc.; R5, R6 = H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclyl, etc.; R7, R8 = H, alkyl; Z = SO0-2], were prepared A composition comprising an ileal bile acid transport inhibitor and an HMG Co-A reductase inhibitor is claimed. Thus, title compound (II) (preparation via 2-mercapto-4-methoxybenzophenone given) at 0.2% as an ileal perfusion in guinea pigs reduced HDL cholesterol from 89 mg% to 76 mg%.

IC ICM A61K031-38
ICS C07D337-12

INCL 514431000

CC 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

IT

178678-22-3P	178678-23-4P	178678-24-5P	178678-25-6P	178678-26-7P
178678-27-8P	178678-28-9P	178678-29-0P	178678-30-3P	178678-31-4P
178678-33-6P	178678-34-7P	178678-35-8P	178678-36-9P	178678-37-0P
178678-38-1P	178678-39-2P	178678-40-5P	178678-43-8P	178678-44-9P
178678-45-0P	178678-48-3P	178678-51-8P	178678-52-9P	178678-53-0P
178678-54-1P	178897-95-5P	178897-96-6P	178897-97-7P	178897-98-8P
178897-99-9P	178898-00-5P	178898-01-6P	178898-02-7P	178898-03-8P

178898-04-9P 178898-05-0P 197372-66-0P 197372-67-1P 197372-69-3P
197372-70-6P 197372-71-7P 197372-72-8P 197372-73-9P 197372-74-0P
197372-75-1P 197372-76-2P 197372-77-3P 197372-78-4P 197372-79-5P
197372-80-8P 197372-81-9P 197372-82-0P 197372-83-1P 197372-84-2P
197372-85-3P 197372-86-4P 197372-87-5P 197372-88-6P 197372-89-7P
197372-90-0P 197372-91-1P 197372-92-2P 197372-93-3P 197372-95-5P
197372-96-6P 197372-99-9P 197373-00-5P 197373-01-6P 197373-02-7P
197373-03-8P 197373-07-2P 197373-08-3P 197373-09-4P 197373-10-7P
197373-11-8P 197373-14-1P 197373-16-3P 197373-17-4P 197373-18-5P
197373-19-6P 197373-20-9P 197373-22-1P 197373-24-3P 197373-25-4P
197373-26-5P 197373-27-6P 197373-28-7P 197373-29-8P 197373-30-1P
197373-31-2P 197373-32-3P **197373-37-8P** 197373-38-9P
197373-39-0P 197373-40-3P 197373-41-4P 197373-45-8P 197373-48-1P
197373-59-4P 197373-60-7P 197373-61-8P 197373-62-9P 197373-63-0P
197373-64-1P 197373-67-4P 197373-68-5P 197373-69-6P 197373-70-9P
197373-71-0P 197373-72-1P 197373-76-5P 197373-77-6P 197373-78-7P
197373-79-8P 197373-80-1P 197373-83-4P 197373-85-6P 197373-87-8P
197373-93-6P 197373-95-8P 197373-97-0P 197373-99-2P 197374-00-8P
197374-01-9P 197374-02-0P 197374-03-1P **197374-04-2P**
197374-06-4P 197374-08-6P 197374-09-7P 197374-10-0P 197374-11-1P
197374-13-3P 197374-14-4P 197374-16-6P 197374-17-7P 197374-18-8P
197374-19-9P 197374-20-2P 197374-21-3P 197374-22-4P 197374-29-1P
197374-30-4P 197374-31-5P 197374-32-6P 197374-34-8P 197374-37-1P
197374-38-2P 197374-39-3P 197374-41-7P 197374-42-8P 197374-43-9P
197374-44-0P 197374-45-1P 197374-48-4P 197374-49-5P 197374-50-8P
197374-51-9P 197374-52-0P 197374-53-1P 197374-54-2P 197374-55-3P
197374-56-4P 197374-57-5P 197374-58-6P **197374-59-7P**
197374-60-0P 197374-62-2P 197374-63-3P 197374-65-5P 197374-66-6P
197374-67-7P 197374-68-8P 197374-69-9P 197374-72-4P 197374-73-5P
197374-74-6P 197374-75-7P 197374-76-8P 197374-77-9P 197374-78-0P
197374-79-1P 197374-80-4P 197374-81-5P 197374-82-6P 197374-83-7P
197374-85-9P 197374-86-0P 197374-87-1P 197374-88-2P 197374-89-3P
197374-90-6P 197374-93-9P 197374-94-0P 197374-95-1P 197374-96-2P
197374-97-3P 197374-98-4P 197374-99-5P 197375-00-1P 197375-01-2P
197375-02-3P 197375-03-4P 197375-04-5P 197375-05-6P 197375-06-7P
197375-07-8P 197375-08-9P 197375-09-0P 197375-10-3P 197375-11-4P
197375-12-5P 197375-13-6P 197375-14-7P 197375-15-8P 197375-16-9P
197375-17-0P 197375-20-5P 197375-21-6P 197375-22-7P 197375-23-8P
197375-24-9P 197375-25-0P 197375-26-1P 197375-28-3P 197375-30-7P
197375-32-9P 197375-34-1P 197375-36-3P 197375-39-6P 197375-42-1P
197375-44-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors)

IT 197375-52-3P 197375-57-8P 197375-60-3P 197375-63-6P 197375-66-9P
197375-68-1P 197375-74-9P 197375-75-0P 197375-80-7P 197375-84-1P
197375-86-3P 197375-89-6P 197375-93-2P 197375-94-3P
197375-96-5P 197376-00-4P 197376-06-0P 197376-07-1P
197376-08-2P 197376-09-3P 197376-10-6P 197376-11-7P 197376-12-8P
197376-13-9P 197376-14-0P 197376-15-1P 197376-17-3P 197376-18-4P
197376-19-5P 197376-20-8P 197376-21-9P 197376-22-0P 197376-25-3P
197376-27-5P 197376-29-7P 197376-31-1P 197376-32-2P 197376-34-4P
197376-36-6P 197376-38-8P 197376-46-8P 197376-49-1P 197376-52-6P
197376-55-9P 197376-58-2P 197376-61-7P 197376-64-0P
197376-67-3P 197376-69-5P 197376-73-1P 197376-74-2P 197376-75-3P
197376-76-4P 197376-77-5P 197376-80-0P 197376-81-1P 197376-82-2P
197376-83-3P 197376-84-4P 197376-85-5P 197376-86-6P 197376-89-9P

197376-90-2P 197376-92-4P 197376-94-6P 197376-95-7P 197376-97-9P
197376-99-1P 197377-02-9P 197377-03-0P 197377-05-2P 197377-09-6P
197377-10-9P 197377-11-0P 197377-12-1P 197377-14-3P 197377-16-5P
197377-17-6P 197377-18-7P 197377-19-8P 197377-20-1P 197377-21-2P
197377-23-4P 197377-24-5P 197377-25-6P 197377-26-7P 197377-27-8P
197377-28-9P 197377-29-0P 197377-30-3P 197377-32-5P 197377-33-6P
197377-34-7P 197377-35-8P 197377-36-9P 197377-37-0P 197377-38-1P
197377-39-2P 197377-40-5P 197377-42-7P 197377-43-8P 197377-45-0P
197377-46-1P 197377-47-2P 197377-48-3P 197377-49-4P 197377-50-7P
197377-51-8P 197377-52-9P 197377-53-0P 197377-54-1P 197377-55-2P
197377-58-5P 197377-60-9P 197377-61-0P 197377-62-1P 197377-63-2P
197377-64-3P 197377-65-4P 197377-66-5P 197377-68-7P 197377-69-8P
197377-70-1P 197377-71-2P 197377-72-3P 197377-73-4P 197377-74-5P
197377-75-6P 197377-76-7P 197377-77-8P 197377-78-9P 197377-79-0P
197377-82-5P 197377-83-6P 197377-84-7P 197377-85-8P 197377-86-9P
197377-90-5P 197377-91-6P 197377-93-8P 197377-94-9P 197377-96-1P
197377-98-3P **197384-36-4P** 197384-39-7P 197390-49-1P
197390-68-4P 213312-50-6P 213312-51-7P 213312-52-8P 213312-53-9P
213312-55-1P 213312-63-1P 213312-67-5P 213312-77-7P 213312-80-2P
213312-81-3P 213312-82-4P 213312-83-5P **213312-84-6P**
213312-86-8P 213312-87-9P 213312-89-1P 213312-90-4P 213312-92-6P
213312-93-7P 213312-94-8P 213312-95-9P 213312-96-0P 213312-97-1P
213312-98-2P 213312-99-3P 213313-00-9P 213313-01-0P 213313-02-1P
213313-03-2P 213313-05-4P 213313-06-5P 213313-07-6P 213313-08-7P
213313-10-1P 213313-11-2P 213313-15-6P 213313-18-9P 213313-19-0P
213313-20-3P 213313-21-4P 213313-22-5P 213313-23-6P
213313-24-7P 213313-25-8P 213313-26-9P 213313-27-0P 213313-28-1P
213313-29-2P 213313-30-5P 213313-31-6P 213313-32-7P 213313-33-8P
213313-34-9P 213313-35-0P 213386-72-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors)

IT 459-46-1P 1515-89-5P 3670-91-5P 24632-01-7P 70132-87-5P
120454-34-4P 120936-00-7P 123501-25-7P 178678-21-2P 178678-55-2P
178678-57-4P 178678-58-5P 178678-59-6P 178678-61-0P 178678-62-1P
178678-64-3P 178678-66-5P 178678-69-8P 178678-70-1P 178678-71-2P
178678-72-3P 178678-73-4P 197373-04-9P 197373-05-0P 197373-42-5P
197373-43-6P 197373-44-7P 197373-46-9P 197373-47-0P 197373-49-2P
197373-50-5P 197373-51-6P 197373-55-0P 197373-56-1P
197373-57-2P 197373-58-3P 197378-05-5P 197378-07-7P 197378-20-4P
197378-22-6P 197378-24-8P 197378-26-0P 197378-29-3P 197378-31-7P
197378-32-8P 197378-34-0P 197378-36-2P 197378-38-4P 197378-40-8P
197378-42-0P 197378-44-2P 197378-46-4P 197378-50-0P 197378-52-2P
197378-54-4P 197378-56-6P 197378-58-8P 213312-68-6P 213312-69-7P
213312-70-0P 213312-72-2P 213312-73-3P **213312-74-4P**
213312-76-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors)

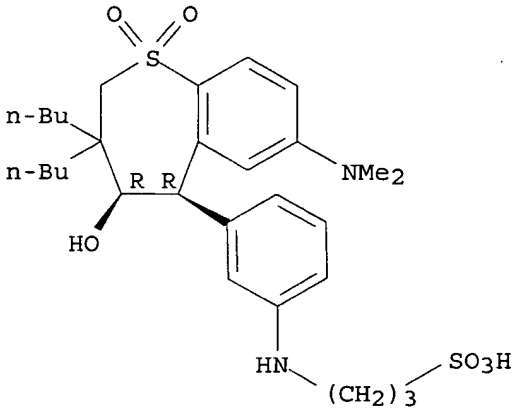
IT **197373-37-8P 197374-04-2P 197374-59-7P**
197375-96-5P 197376-55-9P 197384-36-4P
213312-84-6P 213313-20-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of ileal bile acid transport inhibiting benzothiepines for

combination therapy with HMG Co-A reductase inhibitors)

RN 197373-37-8 HCAPLUS

CN 1-Propanesulfonic acid, 3-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-, rel- (9CI) (CA INDEX NAME)

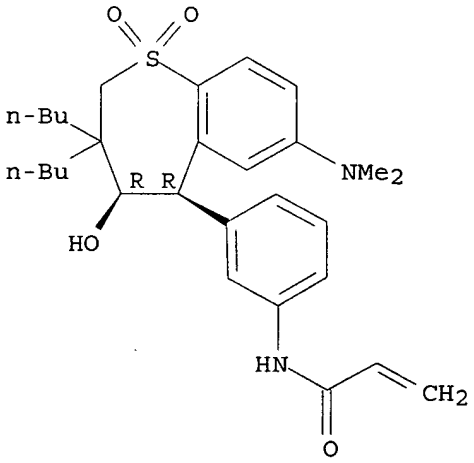
Relative stereochemistry.



RN 197374-04-2 HCAPLUS

CN 2-Propenamide, N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

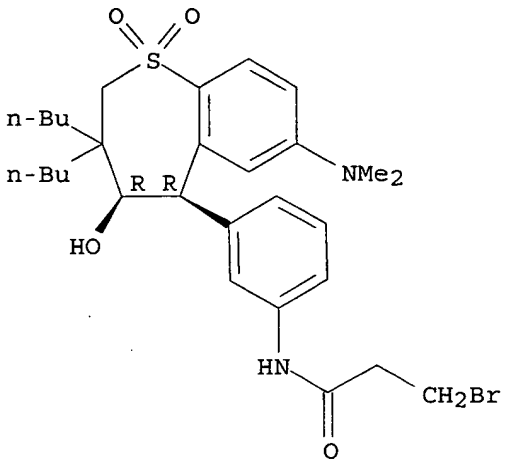
Relative stereochemistry.



RN 197374-59-7 HCAPLUS

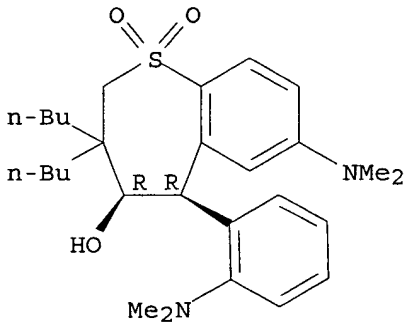
CN Propanamide, 3-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



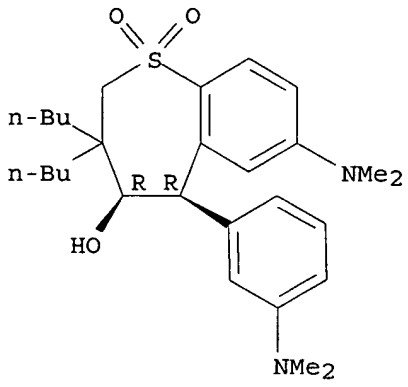
RN 197375-96-5 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[2-(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 197376-55-9 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[3-(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

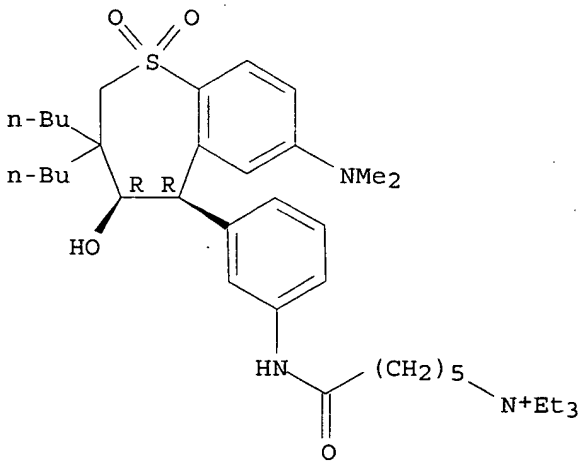


RN 197384-36-4 HCAPLUS
CN 1-Hexanaminium, 6-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-6-oxo-, rel-, salt with trifluoroacetic acid (1:1) (9CI) (CA INDEX NAME)

CM 1

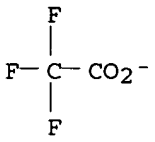
CRN 197384-35-3
CMF C38 H62 N3 O4 S

Relative stereochemistry.



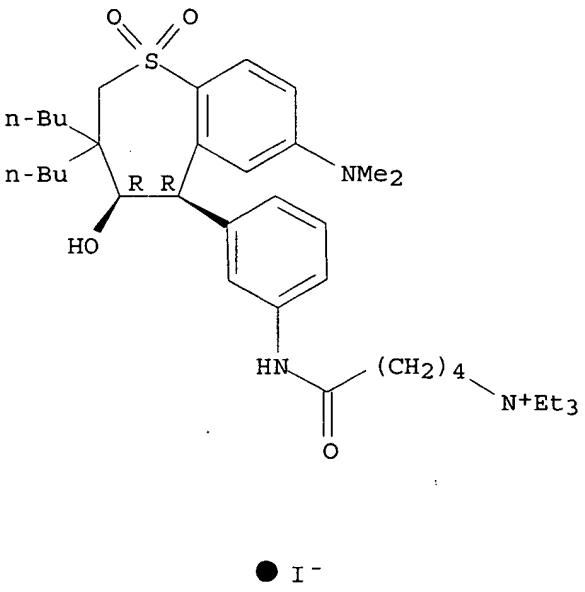
CM 2

CRN 14477-72-6
CMF C2 F3 O2



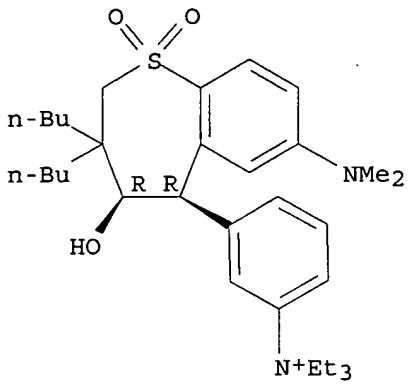
RN 213312-84-6 HCAPLUS
CN 1-Pentanaminium, 5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-oxo-, iodide, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 213313-20-3 HCAPLUS
CN Benzenaminium, 3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]-N,N,N-triethyl-, bromide, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

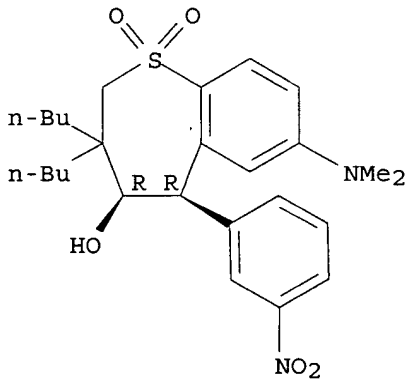


● Br^-

IT **197373-50-5P 197373-51-6P 213312-74-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors)

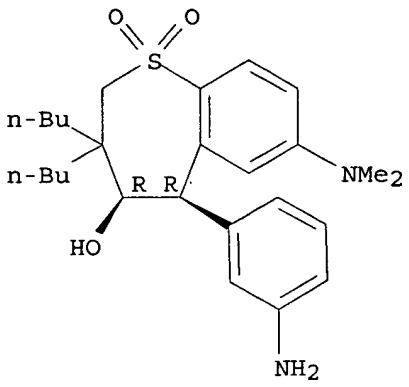
RN 197373-50-5 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



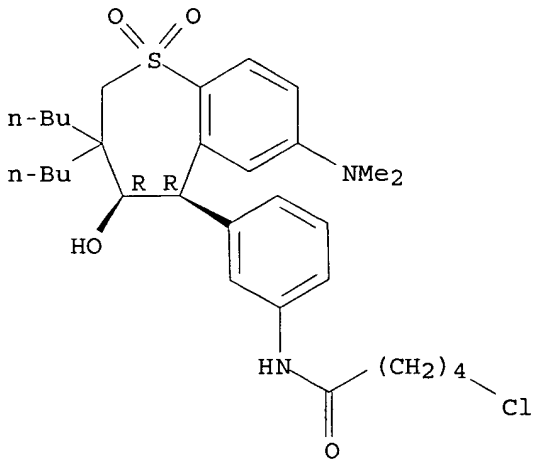
RN 197373-51-6 HCAPLUS
CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 213312-74-4 HCAPLUS
CN Pentanamide, 5-chloro-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:590035 HCAPLUS
DOCUMENT NUMBER: 133:193089
TITLE: Preparation of substituted 5-aryl-benzothiepines as ileal bile acid transport and taurocholate uptake inhibitors
INVENTOR(S): Lee, Len F.; Banerjee, Shyamal C.; Huang, Horng-chih; Li, Jinglin J.; Miller, Raymond E.; Reitz, David B.; Tremont, Samuel J.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA
SOURCE: U.S., 191 pp., Cont.-in-part of U. S. Ser. No. 109,551.
CODEN: USXXAM
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

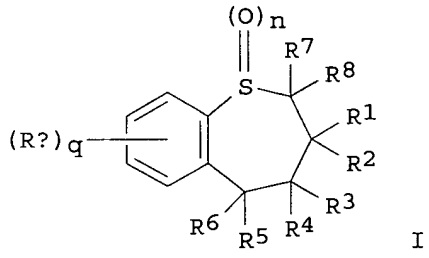
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6107494	A	20000822	US 1999-275463	19990324
CA 2506703	AA	19970918	CA 1997-2506703	19970311
EP 1440972	A1	20040728	EP 2004-10088	19970311
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
US 5994391	A	19991130	US 1998-109551	19980702
EP 1331225	A1	20030730	EP 2003-5459	19981216
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
CA 2336315	AA	20000113	CA 1999-2336315	19990629
WO 2000001687	A1	20000113	WO 1999-US12828	19990629
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9948202	A1	20000124	AU 1999-48202	19990629
AU 766957	B2	20031030		
EP 1091953	A1	20010418	EP 1999-931769	19990629
EP 1091953	B1	20031210		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200100824	T2	20010723	TR 2001-200100824	19990629
BR 9911737	A	20011211	BR 1999-11737	19990629
EE 200100002	A	20020617	EE 2001-2	19990629
JP 2002519418	T2	20020702	JP 2000-558091	19990629
NZ 509621	A	20030829	NZ 1999-509621	19990629
AT 256122	E	20031215	AT 1999-931769	19990629
PT 1091953	T	20040430	PT 1999-931769	19990629
ES 2213373	T3	20040816	ES 1999-931769	19990629
EP 1466911	A2	20041013	EP 2003-26649	19990629
EP 1466911	A3	20050907		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
SG 108309	A1	20050128	SG 2002-200207701	19990629
US 6262277	B1	20010717	US 1999-443403	19991119
TW 229670	B1	20050321	TW 1999-88111293	20000107
AU 761249	B2	20030529	AU 2000-53394	20000816
NO 2001000016	A	20010302	NO 2001-16	20010102
ZA 2001000028	A	20010725	ZA 2001-28	20010102
HR 2001000004	A1	20011231	HR 2001-4	20010102
BG 105206	A	20010928	BG 2001-105206	20010131
US 2002013476	A1	20020131	US 2001-828968	20010409
US 6387924	B2	20020514		
US 2002188119	A1	20021212	US 2002-72600	20020211
US 6875877	B2	20050405		
US 2003171426	A1	20030911	US 2002-76091	20020215
US 6642268	B2	20031104		
AU 2004200346	A1	20040226	AU 2004-200346	20040130
JP 2004203891	A2	20040722	JP 2004-50473	20040225
US 2004204478	A1	20041014	US 2004-830125	20040423
JP 2004359694	A2	20041224	JP 2004-227034	20040803

PRIORITY APPLN. INFO.:

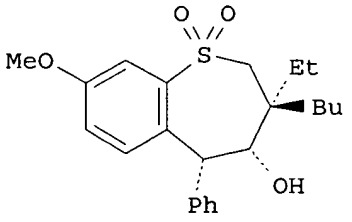
US	1994-305526	B2 19940913
US	1995-517051	B1 19950821
US	1996-13119P	P 19960311
US	1997-816065	B2 19970311
US	1997-831284	B2 19970331
US	1997-68170P	P 19971219
US	1998-109551	A2 19980702
AU	1997-23266	A3 19970311
CA	1997-2248586	A3 19970311
EP	1997-915976	A3 19970311
US	1997-40660P	P 19970311
EP	1998-962044	A3 19981216
US	1999-275463	A1 19990324
EP	1999-931769	A3 19990629
JP	2000-558091	A3 19990629
WO	1999-US12828	W 19990629
US	1999-443403	A1 19991119
US	2000-676466	A3 20000929
US	2000-581897	A3 20001002
US	2001-828968	A3 20010409
US	2002-68297	A3 20020208

OTHER SOURCE(S): MARPAT 133:193089

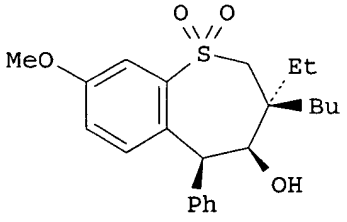
GI



I



II



III

AB The title compds. (I) [wherein q = 1-4; n = 2; R1 and R2 = independently H or (un)substituted (halo)alkyl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy(alkyl), dialkylamino, alkylthio, (polyalkyl)aryl, or cycloalkyl; or R1 and R2 taken together with the atoms to which they are attached = cycloalkyl; R3 and R4 = independently H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocyclyl, OR9, NR9R10, SR9, S(O)R9, SO2R9, or SO3R9; R9 and R10 = independently H, (cyclo)alkyl, alkenyl, alkynyl, aryl(alkyl), acyl, heterocyclyl, or ammoniumalkyl; or R3 and R4 together = :O, :NOR11, :S, :NNR11R12, :NR9, or :CR11R12; R11 and R12 = independently H, (cyclo)alkyl, alkenyl, alkynyl, aryl(alkyl), heterocyclyl, carboxylalkyl, carboalkoxyalkyl, cyanoalkyl, OR9, NR9R10, SR9, S(O)R9, SO2R9, SO3R9, CO2R9, CN, halo, oxo, or CONR9R10; R5 = substituted aryl; R6 = H; R7 and R8 = independently H or alkyl; Rx = independently H or (un)substituted

(cyclo)alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl(alkyl), halo(alkyl), (quaternary) heterocyclyl, (quaternary) heteroaryl, polyether, alkoxy, amino, alkylthio, NO2, carboxy, carbamido, etc.] where prepared for the prophylaxis and treatment of hyperlipidemic conditions, such as those associated with atherosclerosis or hypercholesterolemia. Thus, KOBu-t was added to a solution of 2-((2-benzyl-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (preparation given) and dry THF cooled to -1.6°C to give, after workup, II and III (96% combined yield). The isomers were separated upon recrystn. II inhibited IBAT-mediated uptake of [14C]-taurocholate in H14 cells with an IC50 of 0.1 μM and reduced serum cholesterol from 143 mg (7%) to 126 mg (2%) compared to control in cholesterol-fed hamsters in a 14-day test. In vitro taurocholate uptake assay data are included for nearly 600 compds. of the invention.

IC C07D337-00; C07D487-00; A61K031-38; A61K031-495

INCL 549009000

CC 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

IT 178678-22-3P 178678-23-4P 178678-24-5P 178678-25-6P 178678-26-7P
178678-27-8P 178678-29-0P 178678-33-6P 178678-34-7P 178678-37-0P
178678-46-1P 178678-49-4P 178678-50-7P 178678-51-8P 178678-57-4P
178678-58-5P 178678-59-6P 178897-97-7P 178897-98-8P 178898-00-5P
178898-05-0P 197372-67-1P 197372-71-7P 197372-76-2P 197372-77-3P
197372-78-4P 197373-42-5P 197373-43-6P 197373-44-7P 197373-47-0P
197373-49-2P **197373-50-5P** **197373-51-6P** 197373-55-0P
197373-56-1P 197373-57-2P 197373-58-3P 197375-48-7P 197375-49-8P
289037-96-3P **289037-98-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

IT 178678-28-9P 178678-30-3P 178678-31-4P 178678-35-8P 178678-36-9P
178678-39-2P 178678-40-5P 178678-41-6P 178678-42-7P 178678-43-8P
178678-44-9P 178678-45-0P 178678-47-2P 178678-48-3P 178678-52-9P
178678-53-0P 178678-54-1P 178897-95-5P 178897-96-6P 178897-99-9P
178898-01-6P 178898-02-7P 178898-03-8P 178898-04-9P 197372-66-0P
197372-69-3P 197372-70-6P 197372-72-8P 197372-73-9P 197372-74-0P
197372-75-1P 197372-79-5P 197372-80-8P 197372-81-9P 197372-82-0P
197372-83-1P 197372-84-2P 197372-85-3P 197372-86-4P 197372-87-5P
197372-88-6P 197372-89-7P 197372-90-0P 197372-91-1P 197372-92-2P
197372-93-3P 197372-94-4P 197372-95-5P 197372-96-6P 197372-97-7P
197372-98-8P 197372-99-9P 197373-00-5P 197373-01-6P 197373-02-7P
197373-03-8P 197373-04-9P 197373-05-0P 197373-06-1P 197373-07-2P
197373-08-3P 197373-09-4P 197373-10-7P 197373-11-8P 197373-12-9P
197373-13-0P 197373-14-1P 197373-16-3P 197373-17-4P 197373-18-5P
197373-19-6P 197373-20-9P 197373-22-1P 197373-24-3P 197373-25-4P
197373-26-5P 197373-27-6P 197373-28-7P 197373-29-8P 197373-30-1P
197373-35-6P 197373-36-7P **197373-37-8P** 197373-38-9P
197373-39-0P 197373-40-3P 197373-41-4P 197373-45-8P 197373-48-1P
197373-54-9P 197373-59-4P 197373-60-7P 197373-61-8P
197373-62-9P 197373-63-0P 197373-64-1P 197373-66-3P 197373-67-4P
197373-68-5P 197373-69-6P 197373-70-9P 197373-71-0P 197373-72-1P
197373-73-2P 197373-75-4P 197373-76-5P 197373-77-6P 197373-78-7P
197373-79-8P 197373-80-1P 197373-81-2P 197373-83-4P 197373-85-6P
197373-87-8P 197373-90-3P 197373-93-6P 197373-95-8P 197373-97-0P
197373-99-2P 197374-00-8P 197374-01-9P 197374-02-0P 197374-03-1P

197374-04-2P 197374-06-4P 197374-08-6P 197374-09-7P
197374-10-0P 197374-11-1P 197374-13-3P 197374-14-4P 197374-16-6P
197374-17-7P 197374-18-8P 197374-19-9P 197374-20-2P 197374-21-3P
197374-22-4P 197374-24-6P 197374-25-7P 197374-26-8P 197374-27-9P
197374-29-1P 197374-30-4P 197374-31-5P 197374-32-6P 197374-34-8P
197374-35-9P 197374-37-1P 197374-38-2P 197374-39-3P 197374-40-6P
197374-41-7P 197374-43-9P 197374-44-0P 197374-45-1P 197374-46-2P
197374-47-3P 197374-48-4P 197374-49-5P 197374-50-8P 197374-51-9P
197374-52-0P 197374-53-1P 197374-54-2P 197374-55-3P 197374-56-4P
197374-57-5P 197374-58-6P **197374-59-7P** 197374-60-0P
197374-62-2P 197374-63-3P 197374-64-4P 197374-65-5P 197374-66-6P
197374-67-7P 197374-68-8P 197374-69-9P 197374-71-3P 197374-72-4P
197374-73-5P 197374-74-6P 197374-75-7P 197374-76-8P 197374-77-9P
197374-78-0P 197374-79-1P 197374-80-4P 197374-81-5P 197374-82-6P
197374-83-7P 197374-84-8P 197374-85-9P 197374-86-0P 197374-87-1P
197374-88-2P 197374-89-3P 197374-90-6P 197374-91-7P 197374-92-8P
197374-93-9P 197374-94-0P 197374-95-1P 197374-96-2P 197374-97-3P
197374-98-4P 197374-99-5P 197375-00-1P 197375-01-2P 197375-02-3P
197375-03-4P 197375-04-5P 197375-05-6P 197375-06-7P 197375-07-8P
197375-08-9P 197375-09-0P 197375-10-3P 197375-11-4P 197375-12-5P
197375-13-6P 197375-14-7P 197375-15-8P 197375-16-9P 197375-17-0P
197375-20-5P 197375-22-7P 197375-23-8P 197375-24-9P 197375-25-0P
197375-26-1P 197375-28-3P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

IT 197375-30-7P 197375-32-9P 197375-34-1P 197375-39-6P 197375-42-1P
197375-44-3P 197375-52-3P 197375-57-8P 197375-60-3P 197375-63-6P
197375-66-9P 197375-68-1P 197375-70-5P 197375-72-7P 197375-74-9P
197375-75-0P 197375-80-7P 197375-82-9P 197375-84-1P 197375-86-3P
197375-89-6P 197375-93-2P 197375-94-3P **197375-96-5P**
197375-98-7P 197376-00-4P 197376-02-6P 197376-04-8P 197376-06-0P
197376-07-1P 197376-08-2P 197376-09-3P 197376-10-6P 197376-11-7P
197376-12-8P 197376-13-9P 197376-14-0P 197376-15-1P 197376-17-3P
197376-18-4P 197376-19-5P 197376-21-9P 197376-22-0P 197376-25-3P
197376-31-1P 197376-32-2P 197376-34-4P 197376-36-6P 197376-38-8P
197376-40-2P **197376-42-4P** 197376-46-8P 197376-49-1P
197376-52-6P **197376-55-9P** 197376-58-2P 197376-61-7P
197376-64-0P 197376-67-3P 197376-69-5P 197376-73-1P 197376-74-2P
197376-75-3P 197376-76-4P 197376-77-5P 197376-78-6P 197376-79-7P
197376-81-1P 197376-82-2P 197376-83-3P 197376-84-4P 197376-85-5P
197376-86-6P 197376-88-8P 197376-89-9P 197376-90-2P 197376-92-4P
197376-94-6P 197376-95-7P 197376-97-9P 197376-99-1P 197377-00-7P
197377-02-9P 197377-03-0P 197377-05-2P 197377-09-6P 197377-10-9P
197377-11-0P 197377-12-1P 197377-14-3P 197377-16-5P 197377-17-6P
197377-18-7P 197377-19-8P 197377-20-1P 197377-21-2P 197377-22-3P
197377-23-4P 197377-24-5P 197377-25-6P 197377-26-7P 197377-27-8P
197377-28-9P 197377-29-0P 197377-30-3P 197377-31-4P 197377-32-5P
197377-33-6P 197377-34-7P 197377-35-8P 197377-36-9P 197377-37-0P
197377-38-1P 197377-39-2P 197377-40-5P 197377-42-7P 197377-43-8P
197377-45-0P 197377-46-1P 197377-47-2P 197377-48-3P 197377-49-4P
197377-50-7P 197377-51-8P 197377-53-0P 197377-54-1P 197377-55-2P
197377-57-4P 197377-58-5P 197377-60-9P 197377-61-0P 197377-62-1P
197377-63-2P 197377-64-3P 197377-65-4P 197377-66-5P 197377-68-7P
197377-69-8P 197377-70-1P 197377-71-2P 197377-72-3P 197377-73-4P
197377-74-5P 197377-75-6P 197377-76-7P 197377-77-8P 197377-78-9P

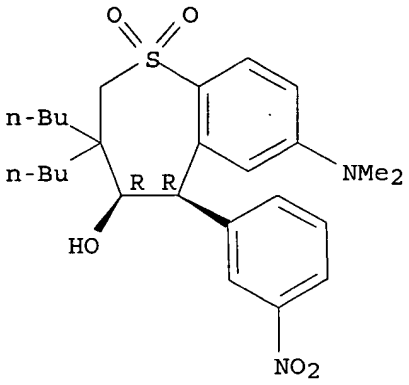
197377-79-0P 197377-81-4P 197377-82-5P 197377-83-6P 197377-84-7P
197377-85-8P 197377-86-9P 197377-90-5P 197377-94-9P 197377-96-1P
197377-98-3P **197384-36-4P** 197384-39-7P 197390-49-1P
197390-68-4P 213312-50-6P 213312-80-2P 213312-99-3P 213313-15-6P
213313-34-9P 213386-72-2P 228113-66-4P 289037-53-2P 289037-54-3P
289037-55-4P 289037-56-5P 289037-57-6P 289037-58-7P 289037-59-8P
289037-60-1P 289037-61-2P 289037-62-3P 289037-64-5P 289037-65-6P
289037-67-8P 289037-68-9P 289037-70-3P 289037-72-5P 289037-74-7P
289037-75-8P 289037-76-9P 289037-77-0P 289037-78-1P 289037-79-2P
289037-80-5P 289037-81-6P 289037-82-7P 289037-83-8P 289037-84-9P
289037-85-0P 289037-86-1P 289037-87-2P 289037-88-3P 289037-90-7P
289037-91-8P 289037-92-9P 289037-93-0P 289037-94-1P 289037-95-2P
289037-97-4P 289037-99-6P 289038-00-2P 289038-01-3P
289038-02-4P 289038-03-5P 289038-04-6P 289038-05-7P 289038-06-8P
289038-07-9P 289038-09-1P 289038-11-5P 289038-13-7P 289038-15-9P
289038-16-0P 289038-18-2P 289038-19-3P 289038-21-7P 289038-23-9P
289038-24-0P 289038-25-1P **289038-26-2P 289038-27-3P**
289038-28-4P 289038-29-5P 289038-30-8P 289038-32-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

IT 289038-33-1P 289038-34-2P **289038-35-3P 289038-36-4P**
289038-37-5P 289038-38-6P 289038-39-7P 289038-40-0P
289038-41-1P 289038-42-2P **289038-43-3P** 289038-44-4P
289038-45-5P 289056-45-7P 289056-46-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

IT **197373-50-5P 197373-51-6P 289037-96-3P**
289037-98-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

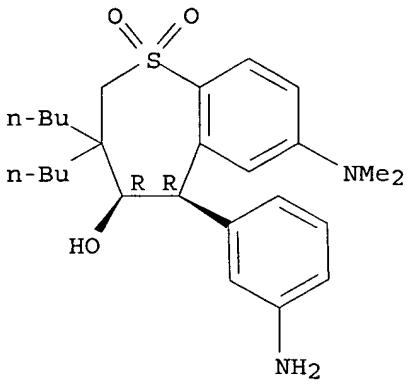
RN 197373-50-5 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



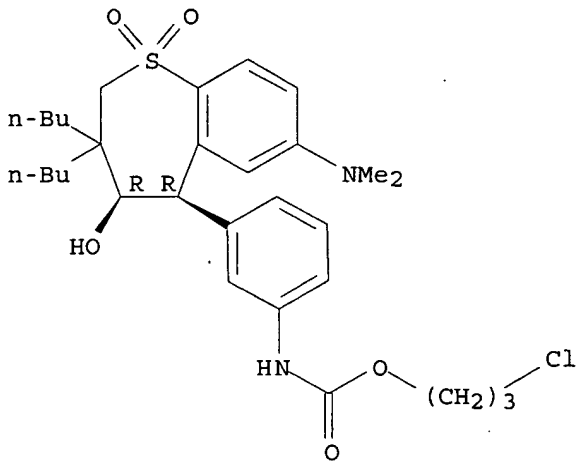
RN 197373-51-6 HCAPLUS
CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



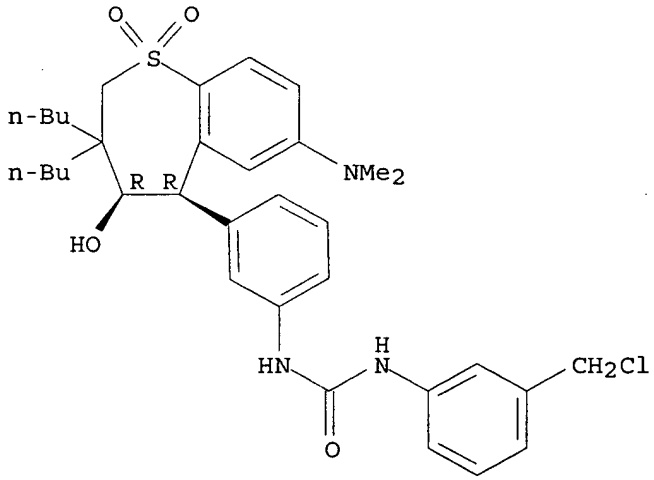
RN 289037-96-3 HCAPLUS
CN Carbamic acid, [3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, 3-chloropropyl ester, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 289037-98-5 HCAPLUS
CN Urea, N-[3-(chloromethyl)phenyl]-N'-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

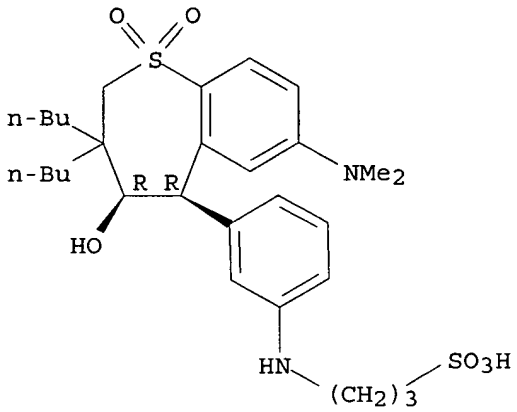
Relative stereochemistry.



IT **197373-37-8P 197373-54-9P 197374-04-2P**
197374-59-7P 197375-96-5P 197376-42-4P
197376-55-9P 197384-36-4P 289037-97-4P
289037-99-6P 289038-26-2P 289038-27-3P
289038-28-4P 289038-35-3P 289038-36-4P
289038-37-5P 289038-38-6P 289038-43-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)
RN 197373-37-8 HCAPLUS
CN 1-Propanesulfonic acid, 3-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-

2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

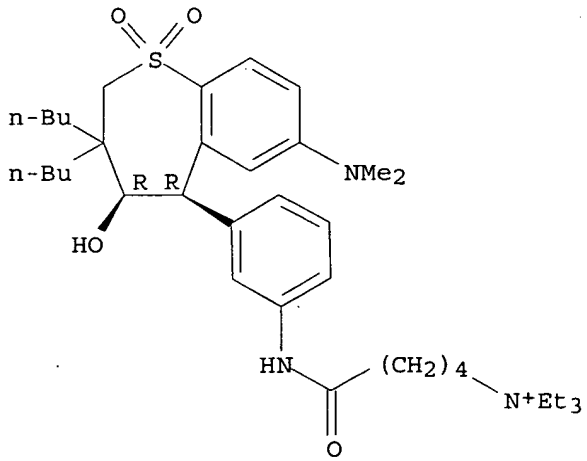


RN 197373-54-9 HCAPLUS
CN 1-Pentanaminium, 5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-oxo-, rel-, salt with trifluoroacetic acid (1:1) (9CI) (CA INDEX NAME)

CM 1

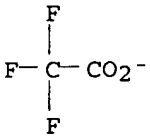
CRN 197373-53-8
CMF C37 H60 N3 O4 S

Relative stereochemistry.



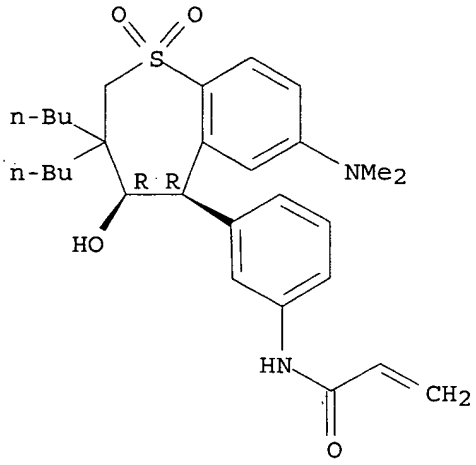
CM 2

CRN 14477-72-6
CMF C2 F3 O2



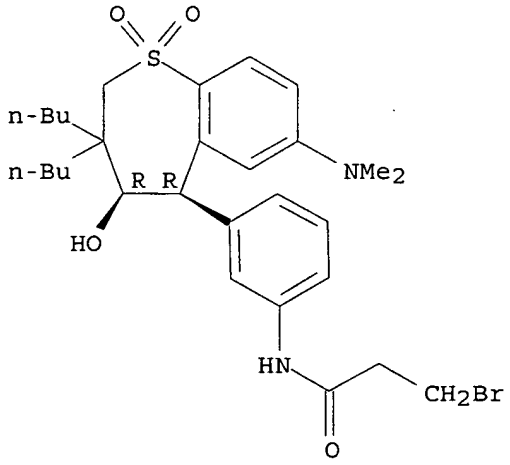
RN 197374-04-2 HCAPLUS
CN 2-Propenamide, N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



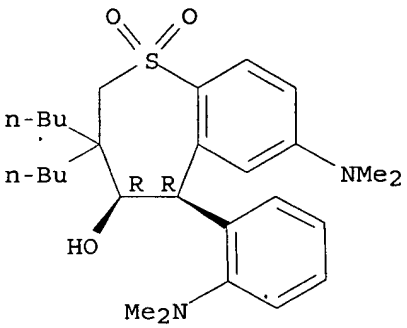
RN 197374-59-7 HCAPLUS
CN Propanamide, 3-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



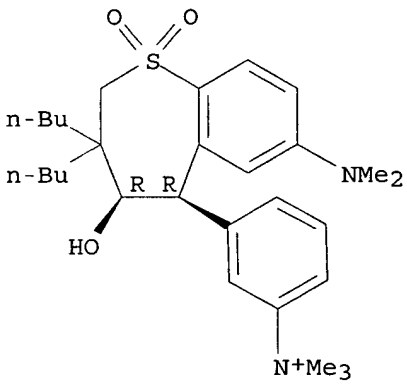
RN 197375-96-5 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[2-(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 197376-42-4 HCAPLUS
CN Benzenaminium, 3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]-N,N,N-trimethyl-, iodide, rel- (9CI) (CA INDEX NAME)

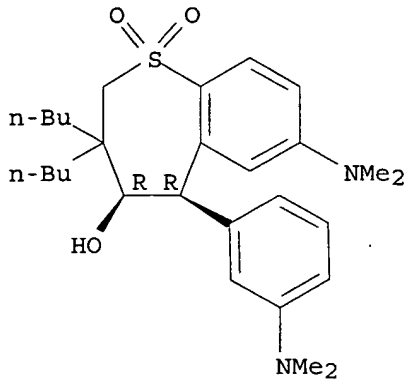
Relative stereochemistry.



● I-

RN 197376-55-9 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[3-(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

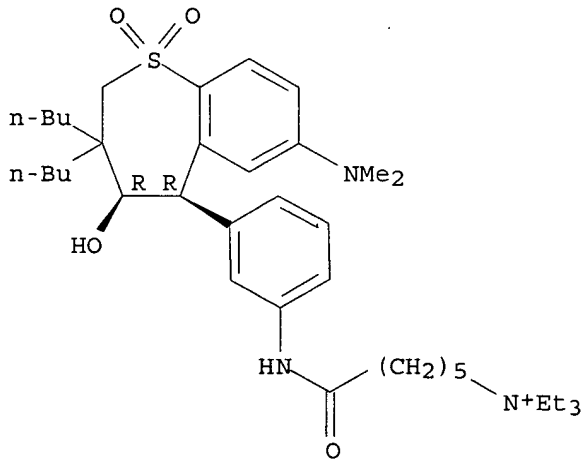


RN 197384-36-4 HCAPLUS
CN 1-Hexanaminium, 6-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-6-oxo-, rel-, salt with trifluoroacetic acid (1:1) (9CI) (CA INDEX NAME)

CM 1

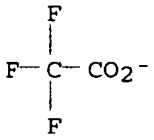
CRN 197384-35-3
CMF C38 H62 N3 O4 S

Relative stereochemistry.



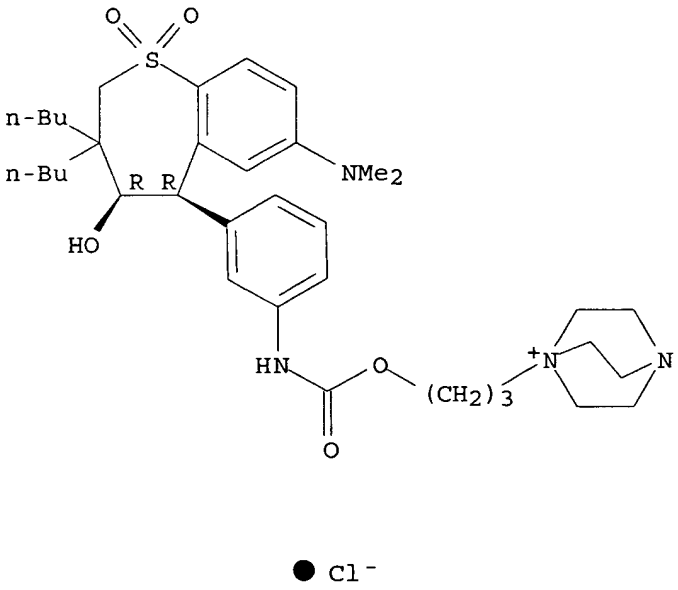
CM 2

CRN 14477-72-6
CMF C2 F3 O2



RN 289037-97-4 HCAPLUS
CN 4-Aza-1-azoniabicyclo[2.2.2]octane, 1-[3-[[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]carbonyl]oxy]propyl]-, chloride, rel- (9CI) (CA INDEX NAME)

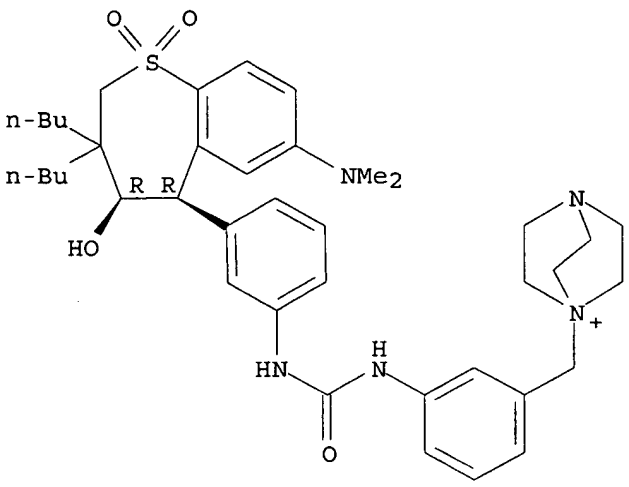
Relative stereochemistry.



● Cl^-

RN 289037-99-6 HCAPLUS
CN 4-Aza-1-azoniabicyclo[2.2.2]octane, 1-[[3-[[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]carbonyl]amino]phenyl]methyl]-, chloride, rel- (9CI) (CA INDEX NAME)

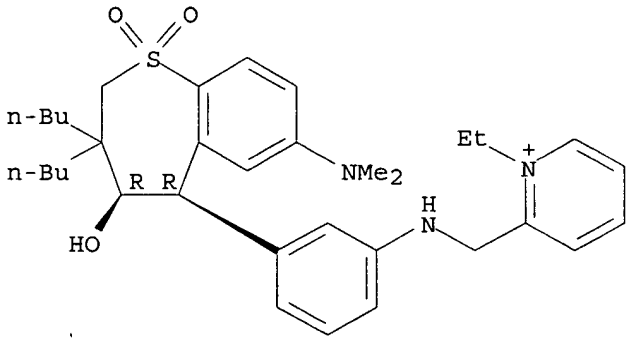
Relative stereochemistry.



● Cl^-

RN 289038-26-2 HCAPLUS
CN Pyridinium, 2-[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]methyl]-1-ethyl-, iodide, rel- (9CI) (CA INDEX NAME)

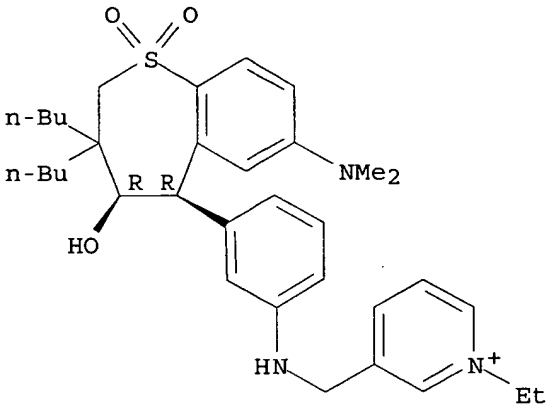
Relative stereochemistry.



● I^-

RN 289038-27-3 HCAPLUS
CN Pyridinium, 3-[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]methyl]-1-ethyl-, iodide, rel- (9CI) (CA INDEX NAME)

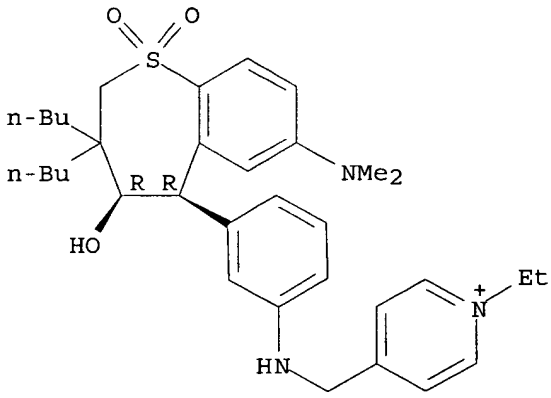
Relative stereochemistry.



● I^-

RN 289038-28-4 HCAPLUS
CN Pyridinium, 4-[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]methyl]-1-ethyl-, iodide, rel- (9CI) (CA INDEX NAME)

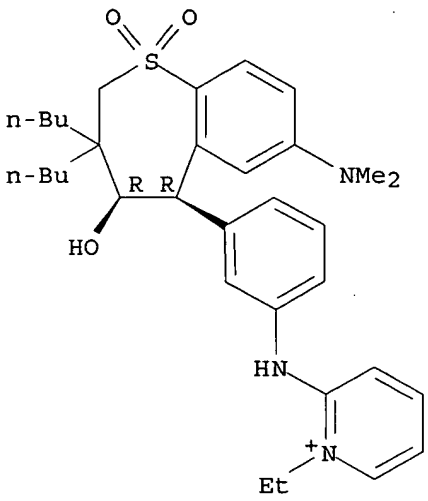
Relative stereochemistry.



● I^-

RN 289038-35-3 HCAPLUS
CN Pyridinium, 2-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-1-ethyl-, iodide, rel- (9CI) (CA INDEX NAME)

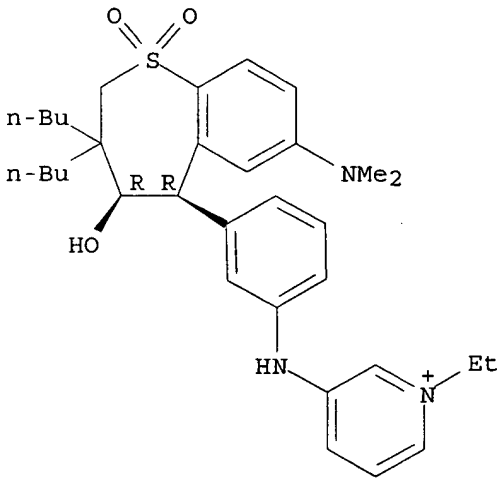
Relative stereochemistry.



● I^-

RN 289038-36-4 HCAPLUS
CN Pyridinium, 3-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-1-ethyl-, iodide, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

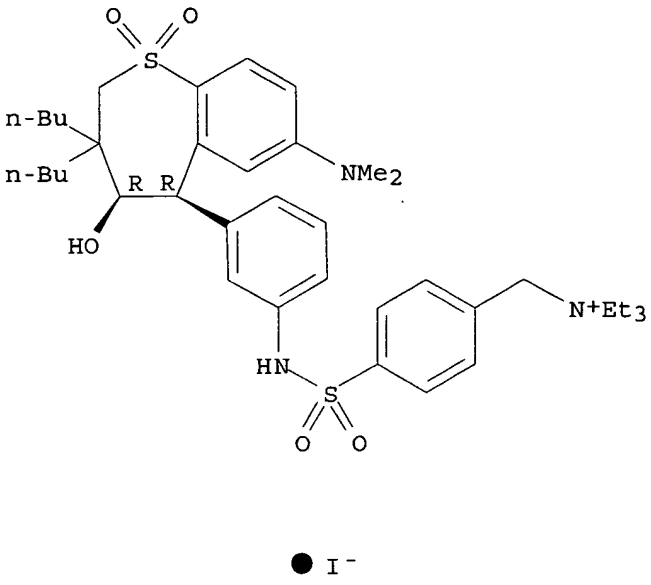


● I^-

RN 289038-37-5 HCAPLUS
CN Benzenemethanaminium, 4-[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]sulfonyl]-N,N,N-triethyl-, iodide, rel- (9CI) (CA INDEX

NAME)

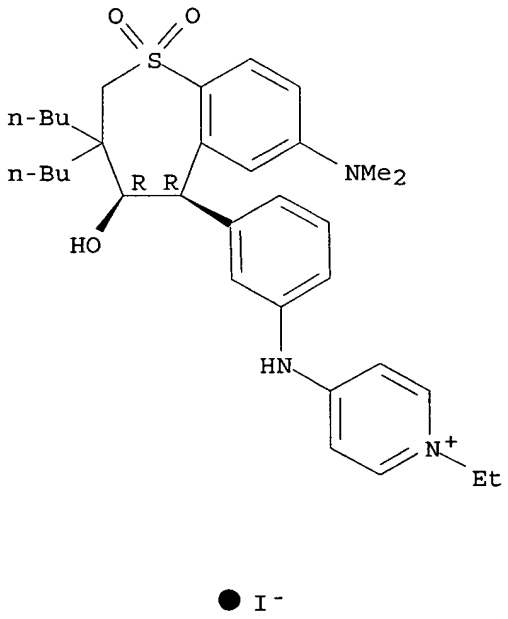
Relative stereochemistry.



● I^-

RN 289038-38-6 HCAPLUS
CN Pyridinium, 4-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-1-ethyl-, iodide, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

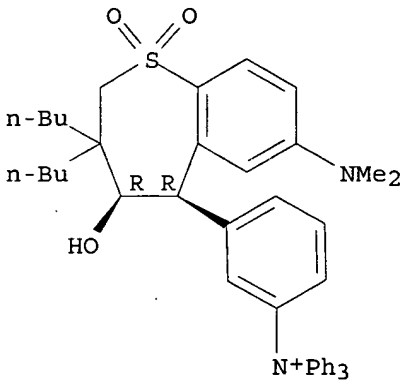


● I^-

RN 289038-43-3 HCAPLUS

CN Benzenaminium, 3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]-N,N,N-triphenyl-, bromide, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● Br^-

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:456922 HCAPLUS
DOCUMENT NUMBER: 133:94515
TITLE: Combinations for cardiovascular indications
INVENTOR(S): Keller, Bradley T.; Reitz, David B.; Schuh, Joseph R.; Sikorski, James A.; Tremont, Samuel J.; Lappe, Rodney W.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA
SOURCE: PCT Int. Appl., 248 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000038725	A1	20000706	WO 1999-US27946	19991217
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2356515	AA	20000706	CA 1999-2356515	19991217
EP 1140187	A1	20011010	EP 1999-965901	19991217
EP 1140187	B1	20030903		

	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO				
BR	9916564	A	20020129	BR 1999-16564	19991217
JP	2002533411	T2	20021008	JP 2000-590676	19991217
EP	1293211	A1	20030319	EP 2002-25631	19991217
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY				
EP	1336413	A1	20030820	EP 2003-9706	19991217
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY				
EP	1340508	A1	20030903	EP 2003-12143	19991217
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
EP	1340509	A1	20030903	EP 2003-12144	19991217
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY				
EP	1340510	A1	20030903	EP 2003-12145	19991217
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
EP	1342475	A1	20030910	EP 2003-11146	19991217
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY				
AT	248606	E	20030915	AT 1999-965901	19991217
EP	1354604	A1	20031022	EP 2003-16600	19991217
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY				
NZ	512532	A	20031219	NZ 1999-512532	19991217
PT	1140187	T	20040130	PT 1999-965901	19991217
ES	2207330	T3	20040516	ES 1999-965901	19991217
AU	779264	B2	20050113	AU 2000-21577	19991217
ZA	2001005056	A	20020620	ZA 2001-5056	20010620
ZA	2001005059	A	20020620	ZA 2001-5059	20010620
ZA	2001005061	A	20020620	ZA 2001-5061	20010620
ZA	2001005062	A	20020828	ZA 2001-5062	20010620
ZA	2001005060	A	20020920	ZA 2001-5060	20010620
NO	2001003157	A	20010822	NO 2001-3157	20010622
US	2003166720	A1	20030904	US 2002-200600	20020723
US	2003203892	A1	20031030	US 2002-200599	20020723
US	2003109558	A1	20030612	US 2002-245506	20020918
US	6890958	B2	20050510		
US	2003125316	A1	20030703	US 2002-245507	20020918
US	2004058908	A1	20040325	US 2002-266743	20021009
US	2004029845	A1	20040212	US 2003-373180	20030226
US	2004028644	A1	20040212	US 2003-412694	20030414
US	2004048846	A1	20040311	US 2003-652306	20030902
PRIORITY APPLN. INFO.:				US 1998-113955P	P 19981223
				US 1999-142603P	P 19990707
				US 1999-142616P	P 19990707
				US 1999-142682P	P 19990707
				US 1999-142684P	P 19990707
				US 1999-143043P	P 19990707
				US 1999-143047P	P 19990707
				US 1999-143550P	P 19990713
				EP 1999-965035	A3 19991217
				EP 1999-965899	A3 19991217
				EP 1999-965900	A3 19991217
				EP 1999-965901	A3 19991217
				EP 1999-965902	A3 19991217
				EP 1999-965903	A3 19991217

EP	1999-967140	A3 19991217
US	1999-465642	A3 19991217
US	1999-466413	A3 19991217
US	1999-466415	A3 19991217
US	1999-466466	B1 19991217
US	1999-466469	A3 19991217
US	1999-466470	A3 19991217
US	1999-466592	A3 19991217
US	1999-466596	B3 19991217
WO	1999-US27946	W 19991217

AB The present invention provides combinations of cardiovascular therapeutic compds. for the prophylaxis or treatment of cardiovascular disease including hypercholesterolemia and atherosclerosis. Combinations disclosed include an ileal bile acid transport inhibitor combined with a cholesteryl ester transport protein (CETP) inhibitor, a fibric acid derivative, a nicotinic acid derivative, a microsomal triglyceride transfer protein inhibitor, a cholesterol absorption antagonist, a phytosterol, a stanol, an antihypertensive agent, or others. Further combinations include a CETP inhibitor with a fibric acid derivative, a nicotinic acid derivative, a bile acid sequestrant, a microsomal triglyceride transfer protein inhibitor, a cholesterol absorption antagonist, or others.

IC ICM A61K045-06
ICS A61K031-55; A61K031-585; A61P009-00; A61K031-575

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

IT 52-01-7, Spironolactone 59-67-6D, Nicotinic acid, derivs 80-97-7, Cholestanol 83-45-4, Fucostanol 360-68-9, Coprostanol 474-60-2, Campestanol 516-95-0, Epicholestanol 943-45-3D, Fibric acid, derivs 4651-51-8 23288-49-5, Probucol 55529-51-6, Clionastanol 96829-58-2, Orlistat 107724-20-9, Eplerenone 114798-26-4, Losartan 138126-65-5, Stigmastanol 163222-33-1 178961-24-5D, enantiomers 197372-90-0D, enantiomers **197373-37-8D**, enantiomers 197373-42-5D, enantiomers 197373-57-2D, enantiomers 229307-33-9D, enantiomers 280105-79-5D, enantiomers 280105-80-8D, enantiomers 280105-82-0D, enantiomers 280105-83-1D, enantiomers 280105-84-2D, enantiomers 280105-85-3D, enantiomers **280105-86-4D**, enantiomers **280105-88-6D**, enantiomers **280105-89-7D**, enantiomers **280105-90-0D**, enantiomers 280105-91-1D, enantiomers 280105-92-2D, enantiomers 280105-94-4D, enantiomers 280105-95-5D, enantiomers 280105-96-6D, enantiomers **280105-97-7D**, enantiomers **280105-98-8D**, enantiomers 280105-99-9D, enantiomers 280106-00-5D, enantiomers 280106-01-6D, enantiomers 280106-02-7D, enantiomers 280106-03-8D, enantiomers 280106-04-9D, enantiomers 280106-05-0D, enantiomers 280106-06-1D, enantiomers 280106-08-3D, enantiomers 280106-09-4D, enantiomers 280106-10-7D, enantiomers 280106-11-8D, enantiomers 280106-12-9D, enantiomers 280106-13-0D, enantiomers
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations for cardiovascular agents for treatment of cardiovascular indications)

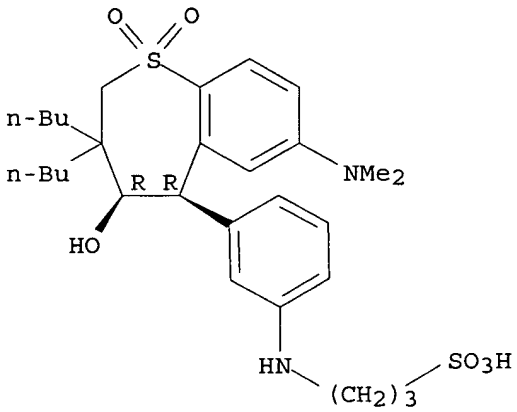
IT **197373-37-8D**, enantiomers **280105-86-4D**, enantiomers **280105-88-6D**, enantiomers **280105-89-7D**, enantiomers **280105-90-0D**, enantiomers **280105-97-7D**, enantiomers **280105-98-8D**, enantiomers
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combinations for cardiovascular agents for treatment of cardiovascular indications)

RN 197373-37-8 HCAPLUS

CN 1-Propanesulfonic acid, 3-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-, rel- (9CI) (CA INDEX NAME)

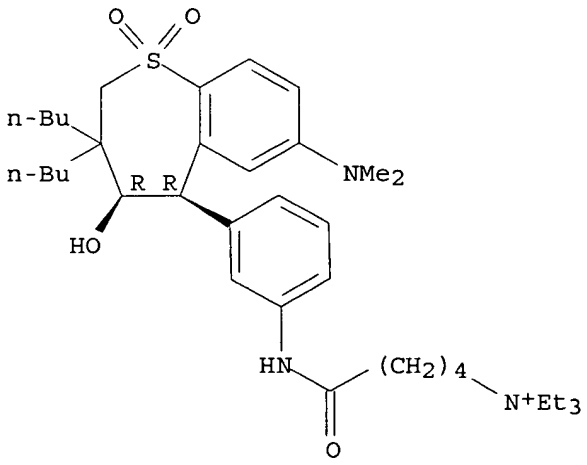
Relative stereochemistry.



RN 280105-86-4 HCAPLUS

CN 1-Pentanaminium, 5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-oxo-, chloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● Cl⁻

RN 280105-88-6 HCAPLUS

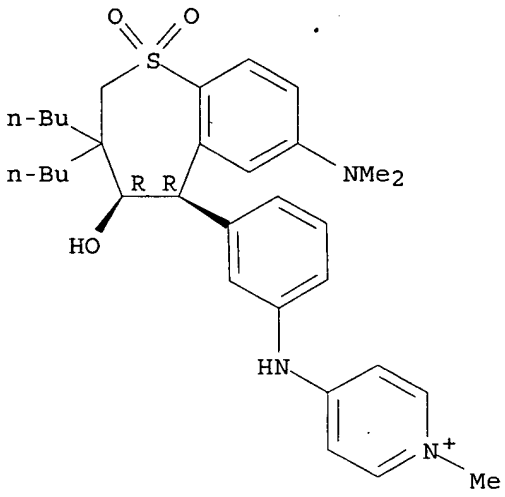
CN Pyridinium, 4-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-1-

methyl-, rel-, salt with 4-methylbenzenesulfonic acid (1:1) (9CI) (CA INDEX NAME)

CM 1

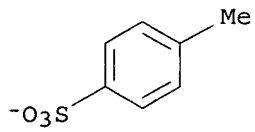
CRN 280105-87-5
CMF C32 H44 N3 O3 S

Relative stereochemistry.



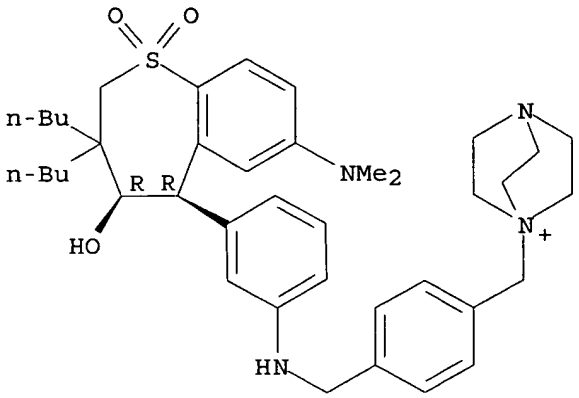
CM 2

CRN 16722-51-3
CMF C7 H7 O3 S



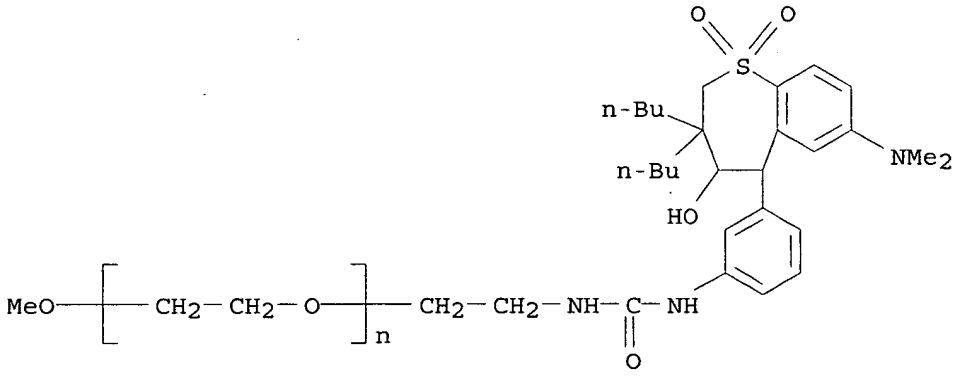
RN 280105-89-7 HCAPLUS
CN 4-Aza-1-azoniabicyclo[2.2.2]octane, 1-[[4-[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]methyl]phenyl]methyl]-, chloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



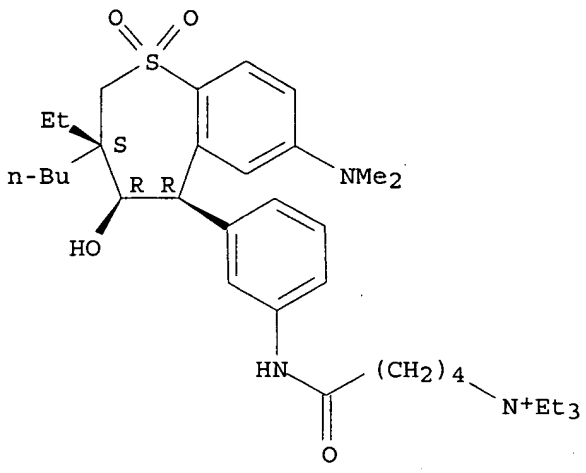
● Cl^-

RN 280105-90-0 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-[2-[[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]carbonyl]amino]ethyl]-ω-methoxy-, rel- (9CI) (CA INDEX NAME)



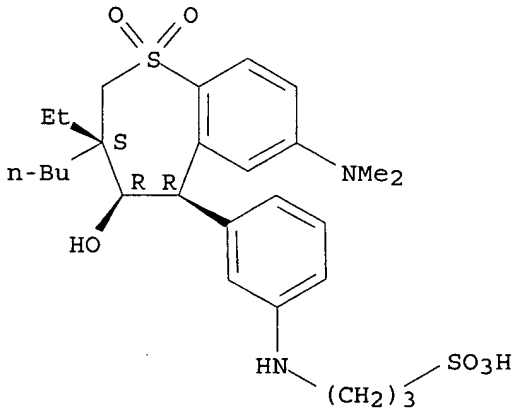
RN 280105-97-7 HCAPLUS
CN 1-Pentanaminium, 5-[[3-[(3R,4S,5S)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-oxo-, chloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 280105-98-8 HCAPLUS
CN 1-Propanesulfonic acid, 3-[[3-[(3R,4S,5S)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:795803 HCAPLUS
DOCUMENT NUMBER: 132:35625
TITLE: Amino acid containing benzo[b]thiepine 1,1-dioxide derivatives as hypolipemic agents
INVENTOR(S): Frick, Wendelin; Enhsen, Alfons; Glombik, Heiner; Heuer, Hubert
PATENT ASSIGNEE(S): Hoechst Marion Roussel Deutschland G.m.b.H., Germany
SOURCE: PCT Int. Appl., 28 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964410	A1	19991216	WO 1999-EP3701	19990528
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19825804	A1	19991216	DE 1998-19825804	19980610
DE 19825804	C2	20000824		
CA 2334775	AA	19991216	CA 1999-2334775	19990528
AU 9945019	A1	19991230	AU 1999-45019	19990528
AU 753275	B2	20021010		
EP 1086092	A1	20010328	EP 1999-927784	19990528
EP 1086092	B1	20021113		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
BR 9912188	A	20010410	BR 1999-12188	19990528
TR 200003634	T2	20010621	TR 2000-200003634	19990528
JP 2002517491	T2	20020618	JP 2000-553419	19990528
AT 227715	E	20021115	AT 1999-927784	19990528
ES 2182535	T3	20030301	ES 1999-927784	19990528
PT 1086092	T	20030331	PT 1999-927784	19990528
RU 2215001	C2	20031027	RU 2001-101491	19990528
CN 1127497	B	20031112	CN 1999-807171	19990528
TR 200003632	T2	20010420	TR 2000-200003632	19990529
PT 1086113	T	20040630	PT 1999-927802	19990529
ES 2215387	T3	20041001	ES 1999-927802	19990529
AU 761249	B2	20030529	AU 2000-53394	20000816
ZA 2000007060	A	20010718	ZA 2000-7060	20001130
ZA 2000007061	A	20010718	ZA 2000-7061	20001130
US 6387944	B1	20020514	US 2000-719047	20001207
US 2002045583	A1	20020418	US 2001-773772	20010202
US 6441022	B2	20020827		
HK 1036799	A1	20040402	HK 2001-107735	20011106

PRIORITY APPLN. INFO.:

DE 1998-19825804	A	19980610
AU 1997-23266	A3	19970311
WO 1999-EP3701	W	19990528
US 1999-398315	A1	19990920

OTHER SOURCE(S): MARPAT 132:35625
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. such as I (mixture of diastereoisomers) were prepared as hypolipemic agents. Thus, I was prepared in 2 sequences from racemic II and Fmoc-D-lys(Boc)-OH, followed by removal of the Fmoc group with Et2NH. I was ≥20 times more active than 3 analogous comparison substances in

tests of fecal separation of 14C-taurocholic acid in rats.

IC ICM C07D337-08
ICS C07K005-068; A61K031-38

CC 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

IT **252372-02-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(amino acid containing benzo[b]thiepine 1,1-dioxide derivs. as hypolipemic agents)

IT 92122-45-7 **252047-42-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(amino acid containing benzo[b]thiepine 1,1-dioxide derivs. as hypolipemic agents)

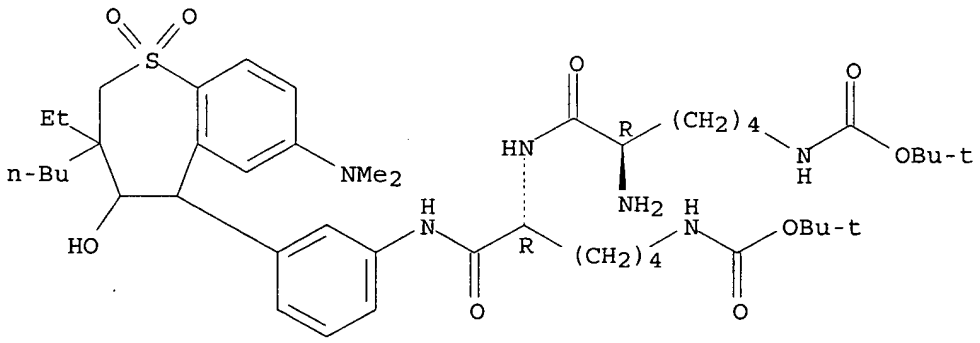
IT **252372-00-2P 252372-01-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(amino acid containing benzo[b]thiepine 1,1-dioxide derivs. as hypolipemic agents)

IT **252372-02-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(amino acid containing benzo[b]thiepine 1,1-dioxide derivs. as hypolipemic agents)

RN 252372-02-4 HCAPLUS

CN D-Lysinamide, N6-[(1,1-dimethylethoxy)carbonyl]-D-lysyl-N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N6-[(1,1-dimethylethoxy)carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

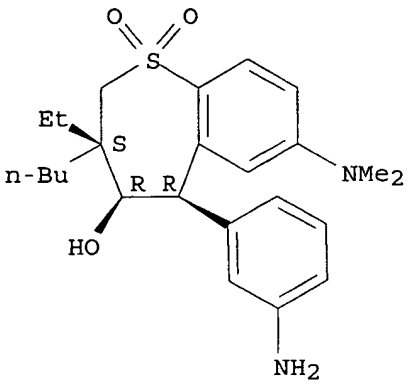


IT **252047-42-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(amino acid containing benzo[b]thiepine 1,1-dioxide derivs. as hypolipemic agents)

RN 252047-42-0 HCAPLUS

CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-, 1,1-dioxide, (3R,4S,5S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

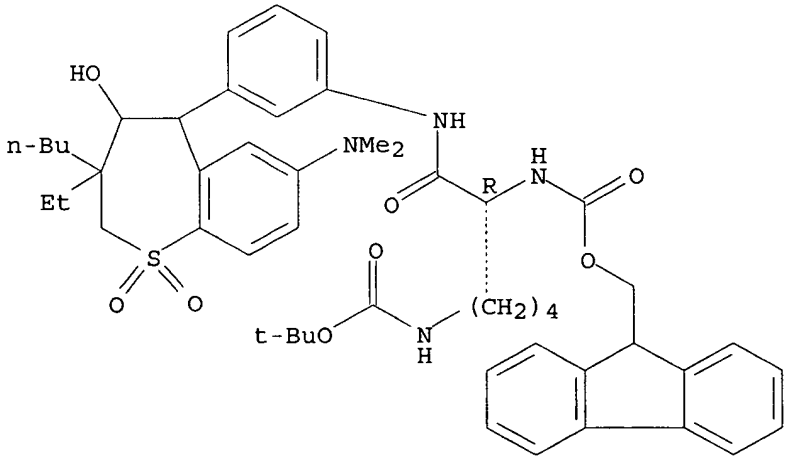


IT **252372-00-2P 252372-01-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(amino acid containing benzo[b]thiepine 1,1-dioxide derivs. as hypolipemic agents)

RN 252372-00-2 HCAPLUS

CN Carbamic acid, [(1R)-1-[[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]carbonyl]-5-[[(1,1-dimethylethoxy)carbonyl]amino]pentyl]-, 9H-fluoren-9-ylmethyl ester (9CI) (CA INDEX NAME)

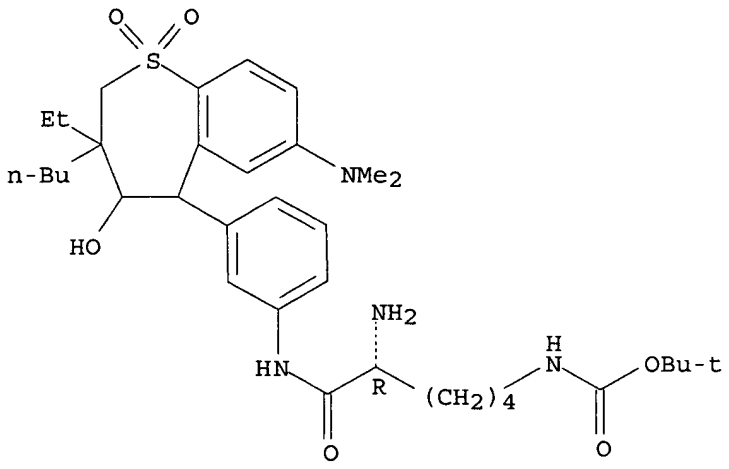
Absolute stereochemistry.



RN 252372-01-3 HCAPLUS

CN Carbamic acid, [(5R)-5-amino-6-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-6-oxohexyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

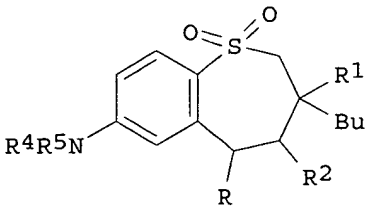
L9 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:795802 HCAPLUS
DOCUMENT NUMBER: 132:22884
TITLE: Preparation of benzothiepine-1,1-dioxides as hypolipemics
INVENTOR(S): Frick, Wendelin; Enhsen, Alfons; Glombik, Heiner; Heuer, Hubert
PATENT ASSIGNEE(S): Hoechst Marion Roussel Deutschland G.m.b.H., Germany
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964409	A2	19991216	WO 1999-EP3743	19990529
WO 9964409	A3	20000302		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19825804	A1	19991216	DE 1998-19825804	19980610
DE 19825804	C2	20000824		
TR 200003634	T2	20010621	TR 2000-200003634	19990528
ES 2182535	T3	20030301	ES 1999-927784	19990528
PT 1086092	T	20030331	PT 1999-927784	19990528
CN 1127497	B	20031112	CN 1999-807171	19990528
CA 2334773	AA	19991216	CA 1999-2334773	19990529
AU 9945031	A1	19991230	AU 1999-45031	19990529
AU 752633	B2	20020926		
EP 1086113	A2	20010328	EP 1999-927802	19990529

EP 1086113	B1	20040211			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI					
TR 200003632	T2	20010420	TR 2000-200003632		19990529
JP 2002517490	T2	20020618	JP 2000-553418		19990529
JP 3374129	B2	20030204			
NZ 508681	A	20020628	NZ 1999-508681		19990529
RU 2220141	C2	20031227	RU 2001-101499		19990529
AT 259372	E	20040215	AT 1999-927802		19990529
PT 1086113	T	20040630	PT 1999-927802		19990529
IL 140078	A1	20040831	IL 1999-140078		19990529
ES 2215387	T3	20041001	ES 1999-927802		19990529
BR 9911123	A	20060103	BR 1999-11123		19990529
US 6221897	B1	20010424	US 1999-398315		19990920
AU 761249	B2	20030529	AU 2000-53394		20000816
ZA 2000007060	A	20010718	ZA 2000-7060		20001130
ZA 2000007061	A	20010718	ZA 2000-7061		20001130
NO 2000006251	A	20010207	NO 2000-6251		20001208
US 2002045583	A1	20020418	US 2001-773772		20010202
US 6441022	B2	20020827			
HK 1039490	A1	20041210	HK 2001-107746		20011106
US 2003017996	A1	20030123	US 2002-201050		20020724
US 6642269	B2	20031104			
US 2004087648	A1	20040506	US 2003-606771		20030627
US 7019023	B2	20060328			
PRIORITY APPLN. INFO.:			DE 1998-19825804	A	19980610
			US 1996-13119P	P	19960311
			AU 1997-23266	A3	19970311
			WO 1999-EP3743	W	19990529
			US 1999-398315	A1	19990920
			US 2001-773772	A1	20010202
			US 2002-201050	A1	20020724

OTHER SOURCE(S): MARPAT 132:22884

GI



I

AB Title compds. [I; R = C6H4NHZR3; R1,R4,R5 = Me, Et, Pr, Bu; R2 = H, OH, amino(alkyl); R3 = sugar residue; Z = bond, carbonyl(alkylene), CONH, etc.] were prepared Thus, I [R = C6H4(NHR')-3, R1 = Et, R2 = OH, R4 = R5 = Me](II; R' = H) was amidated by penta-O-acetyl-D-gluconic acid and the product deprotected to give II (R' = gluconoyl) as a mixture of diastereomers. Data for biol. activity of I were given.

IC ICM C07D337-00

CC 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

IT **252047-36-2P 252047-37-3P 252047-38-4P**
252047-39-5P 252047-40-8P 252047-41-9P
252208-66-5P 252208-67-6P 252208-68-7P
252208-69-8P 252208-70-1P 252208-71-2P

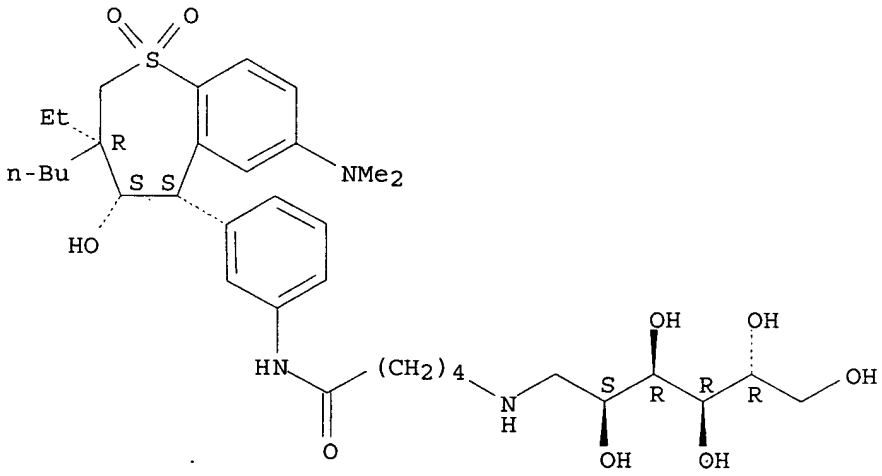
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzothiepine-1,1-dioxides as hypolipemics)

IT 488-43-7, D-Glucamine 2432-99-7, 11-Aminoundecanoic acid 17430-71-6, Penta-O-acetyl-D-gluconic acid 53555-69-4 **252047-42-0** **252047-43-1**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of benzothiepine-1,1-dioxides as hypolipemics)

IT **252047-36-2P** **252047-37-3P** **252047-38-4P** **252047-39-5P** **252047-40-8P** **252047-41-9P** **252208-66-5P** **252208-67-6P** **252208-68-7P** **252208-69-8P** **252208-70-1P** **252208-71-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzothiepine-1,1-dioxides as hypolipemics)

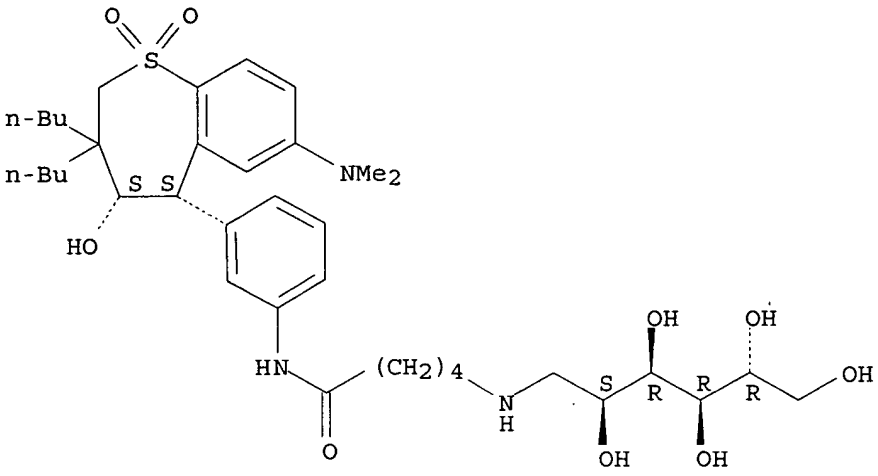
RN 252047-36-2 HCAPLUS
CN D-Glucitol, 1-[[5-[[3-[(3R,4S,5S)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]amino]-1-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



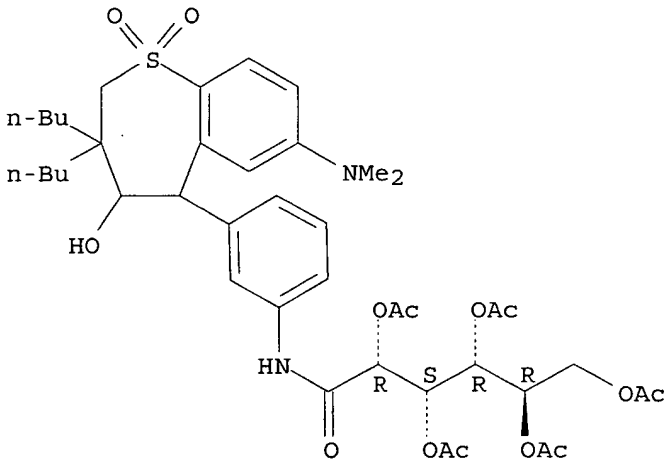
RN 252047-37-3 HCAPLUS
CN D-Glucitol, 1-deoxy-1-[[5-[[3-[(4S,5S)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



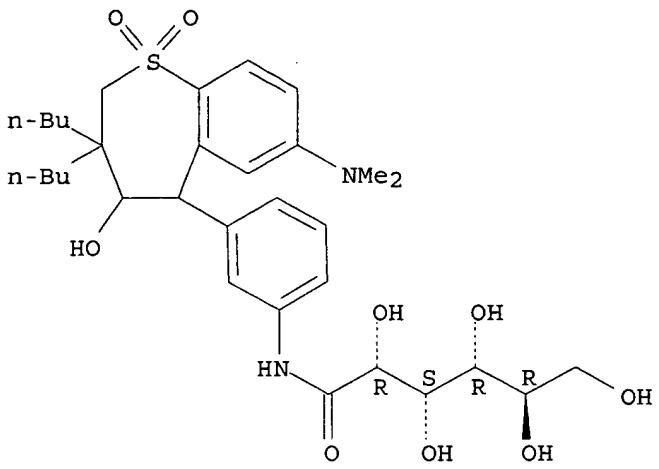
RN 252047-38-4 HCAPLUS
CN D-Gluconamide, N-[3-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, 2,3,4,5,6-pentaacetate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



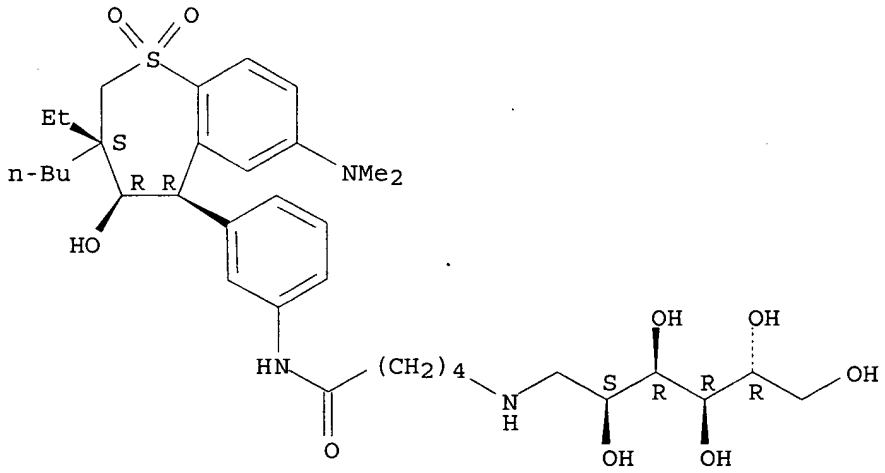
RN 252047-39-5 HCAPLUS
CN D-Gluconamide, N-[3-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



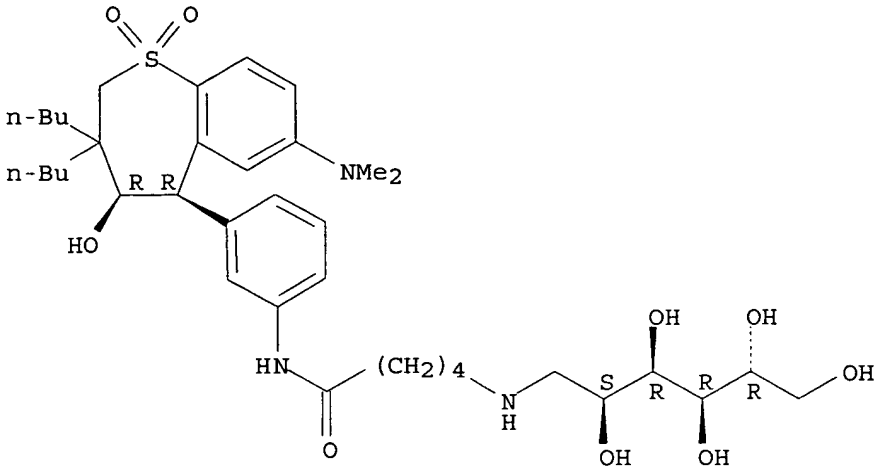
RN 252047-40-8 HCAPLUS
CN D-Glucitol, 1-[[5-[[3-[(3S,4R,5R)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]amino]-1-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



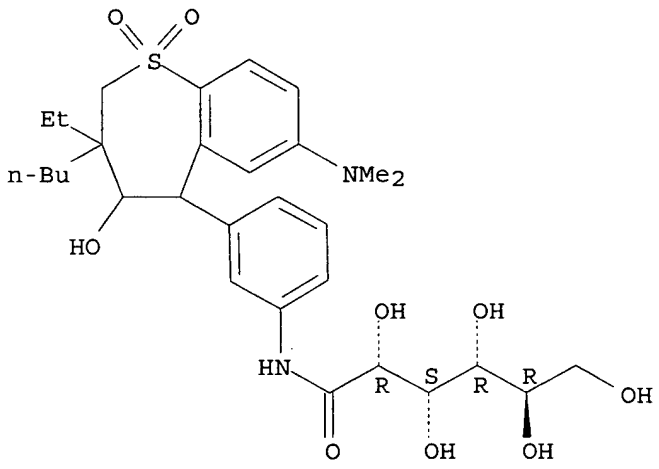
RN 252047-41-9 HCAPLUS
CN D-Glucitol, 1-deoxy-1-[[5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



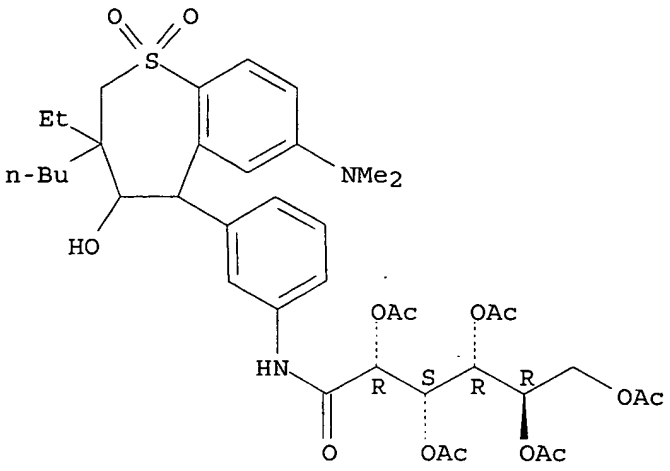
RN 252208-66-5 HCAPLUS
CN D-Gluconamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



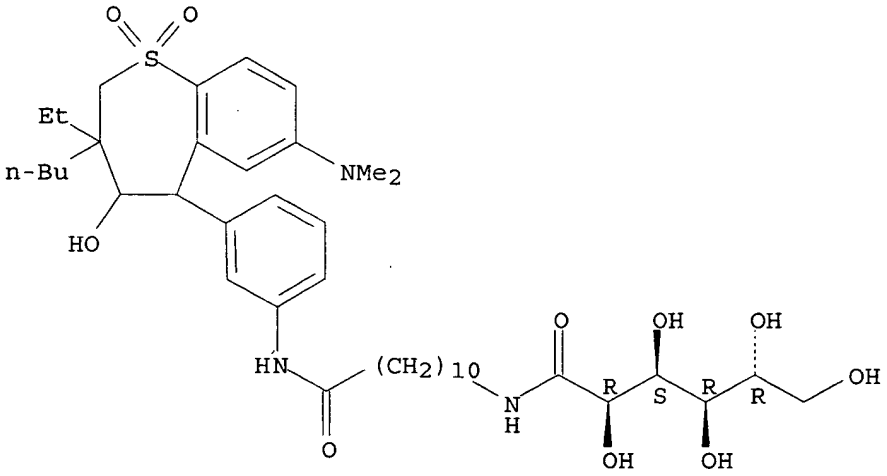
RN 252208-67-6 HCAPLUS
CN D-Gluconamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, 2,3,4,5,6-pentaacetate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



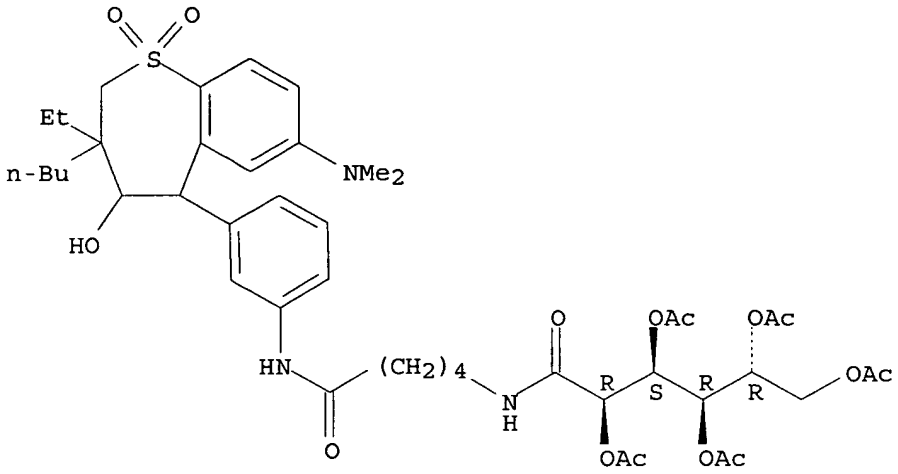
RN 252208-68-7 HCAPLUS
CN D-Gluconamide, N-[11-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-11-oxoundecyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



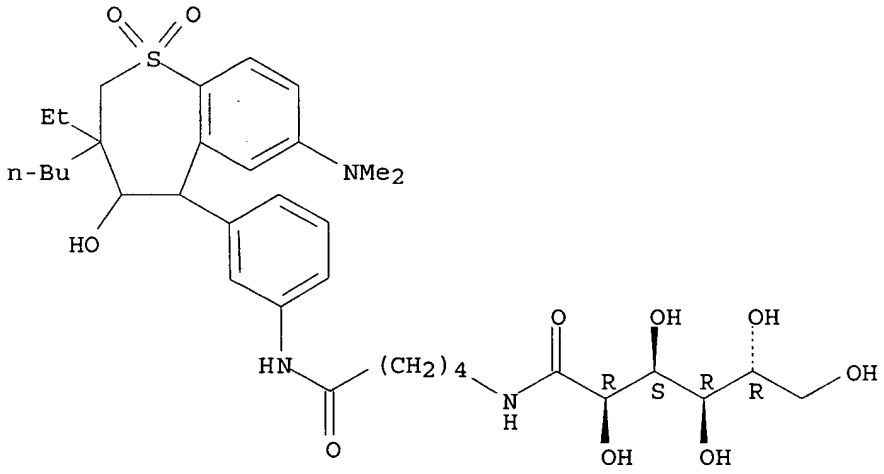
RN 252208-69-8 HCAPLUS
CN D-Gluconamide, N-[5-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]-, 2,3,4,5,6-pentaacetate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



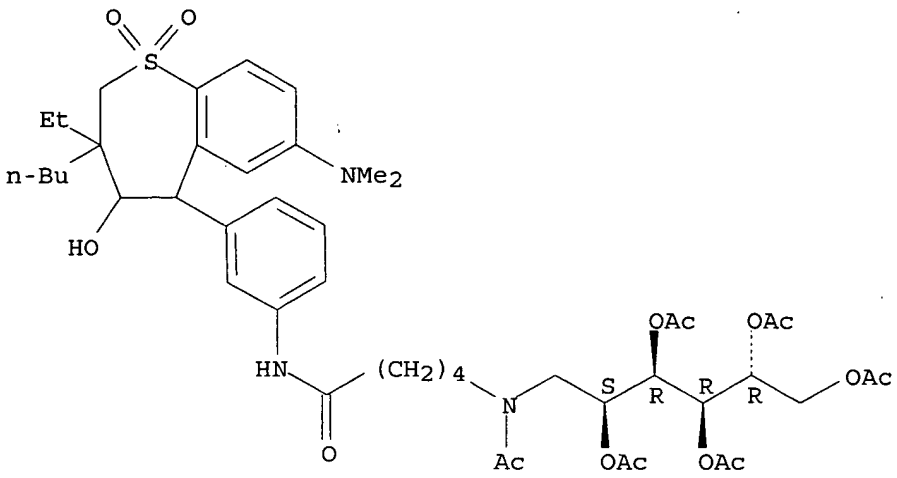
RN 252208-70-1 HCAPLUS
CN D-Gluconamide, N-[5-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



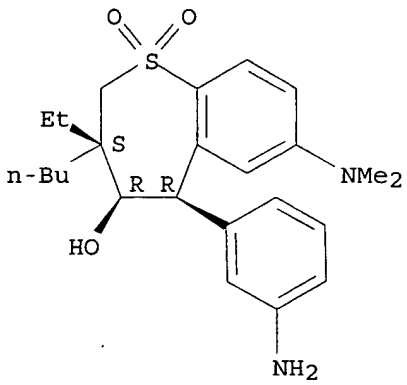
RN 252208-71-2 HCAPLUS
CN D-Glucitol, 1-[acetyl[5-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]amino]-1-deoxy-, 2,3,4,5,6-pentaacetate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



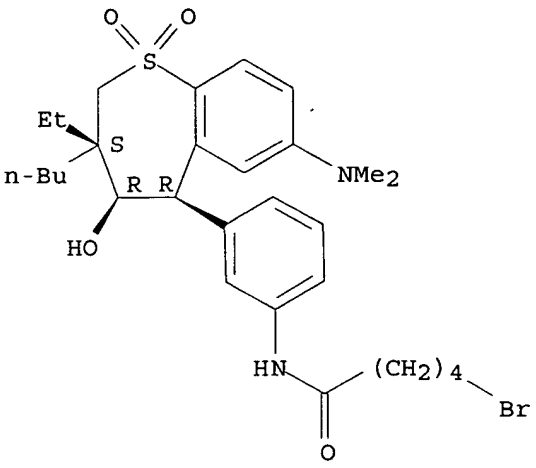
IT **252047-42-0 252047-43-1**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of benzothiepine-1,1-dioxides as hypolipemics)
RN 252047-42-0 HCAPLUS
CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-, 1,1-dioxide, (3R,4S,5S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 252047-43-1 HCAPLUS
CN Pentanamide, 5-bromo-N-[3-[(3R,4S,5S)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



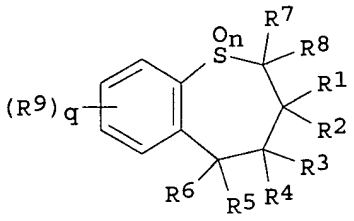
L9 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:621210 HCAPLUS
DOCUMENT NUMBER: 129:260353
TITLE: Preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors.
INVENTOR(S): Reitz, David B.; Lee, Len F.; Li, Jinglin J.; Huang, Horng-Chih; Tremont, Samuel J.; Miller, Raymond E.; Baneriee, Shyamal C.; Manning, Robert E.; Glenn, Kevin C.; Keller, Bradley T.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA; et al.
SOURCE: PCT Int. Appl., 477 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9840375	A2	19980917	WO 1998-US3792	19980310
WO 9840375	A3	19981203		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2283575	AA	19980917	CA 1998-2283575	19980310
AU 9864408	A1	19980929	AU 1998-64408	19980310
AU 730024	B2	20010222		
EP 971744	A2	20000119	EP 1998-910075	19980310
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NZ 337830	A	20010727	NZ 1998-337830	19980310
BR 9808013	A	20010925	BR 1998-8013	19980310
JP 2002500628	T2	20020108	JP 1998-539594	19980310

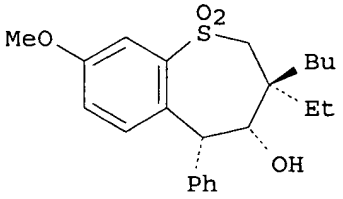
RU 2247579	C2	20050310	RU 1999-121514		19980310
NO 9904390	A	19991104	NO 1999-4390		19990910
AU 761249	B2	20030529	AU 2000-53394		20000816
US 2003171426	A1	20030911	US 2002-76091		20020215
US 6642268	B2	20031104			
PRIORITY APPLN. INFO.:			US 1997-40660P	P	19970311
			US 1994-305526	B2	19940913
			US 1995-517051	B1	19950821
			US 1996-13119P	P	19960311
			AU 1997-23266	A3	19970311
			US 1997-816065	B2	19970311
			US 1997-831284	B3	19970331
			WO 1998-US3792	W	19980310
			US 2000-676466	A3	20000929

OTHER SOURCE(S): MARPAT 129:260353

GI



I



II

AB Title compds. [I; q = 1-4; n = 0-2; R1, R2 = H, (substituted) alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, alkoxy, dialkylamino, etc.; R1R2C = cycloalkylidene; R3, R4 = H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocyclyl, heteroaryl, etc.; R3R4 = O, S, NOR11, etc.; R11 = H, alkyl, alkenyl, alkynyl, aryl, aralkyl, etc.; R5, R6 = H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclyl, etc.; R7, R8 = H, alkyl; R9 = H, alkyl, alkenyl, alkynyl, acyloxy, aryl, aralkyl, halo, etc.], were prepared A composition comprising an ileal bile acid transport inhibitor and an HMG Co-A reductase inhibitor is claimed. Thus, title compound (II) (preparation via 2-mercapto-4-methoxybenzophenone given) at 0.2% as an ileal perfusion in guinea pigs reduced HDL cholesterol from 89 mg% to 76 mg%.

IC ICM C07D337-00

CC 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

IT 178678-22-3P 178678-23-4P 178678-24-5P 178678-25-6P 178678-26-7P
178678-27-8P 178678-28-9P 178678-29-0P 178678-30-3P 178678-31-4P
178678-33-6P 178678-34-7P 178678-35-8P 178678-36-9P 178678-37-0P
178678-38-1P 178678-39-2P 178678-40-5P 178678-43-8P 178678-44-9P
178678-45-0P 178678-48-3P 178678-51-8P 178678-52-9P 178678-53-0P
178678-54-1P 178897-95-5P 178897-96-6P 178897-97-7P 178897-98-8P
178897-99-9P 178898-00-5P 178898-01-6P 178898-02-7P 178898-03-8P
178898-04-9P 178898-05-0P 197372-66-0P 197372-67-1P 197372-69-3P
197372-70-6P 197372-71-7P 197372-72-8P 197372-73-9P 197372-74-0P
197372-75-1P 197372-76-2P 197372-77-3P 197372-78-4P 197372-79-5P
197372-80-8P 197372-81-9P 197372-82-0P 197372-83-1P 197372-84-2P
197372-85-3P 197372-86-4P 197372-87-5P 197372-88-6P 197372-89-7P
197372-90-0P 197372-91-1P 197372-92-2P 197372-93-3P 197372-95-5P
197372-96-6P 197372-99-9P 197373-00-5P 197373-01-6P 197373-02-7P
197373-03-8P 197373-07-2P 197373-08-3P 197373-09-4P 197373-10-7P
197373-11-8P 197373-14-1P 197373-16-3P 197373-17-4P 197373-18-5P

197373-19-6P 197373-20-9P 197373-22-1P 197373-24-3P 197373-25-4P
197373-26-5P 197373-27-6P 197373-28-7P 197373-29-8P 197373-30-1P
197373-31-2P 197373-32-3P **197373-37-8P** 197373-38-9P
197373-39-0P 197373-40-3P 197373-41-4P 197373-45-8P 197373-48-1P
197373-59-4P 197373-60-7P 197373-61-8P 197373-62-9P 197373-63-0P
197373-64-1P 197373-67-4P 197373-68-5P 197373-69-6P 197373-70-9P
197373-71-0P 197373-72-1P 197373-76-5P 197373-77-6P 197373-78-7P
197373-79-8P 197373-80-1P 197373-83-4P 197373-85-6P 197373-87-8P
197373-93-6P 197373-95-8P 197373-97-0P 197373-99-2P 197374-00-8P
197374-01-9P 197374-02-0P 197374-03-1P **197374-04-2P**
197374-06-4P 197374-08-6P 197374-09-7P 197374-10-0P 197374-11-1P
197374-13-3P 197374-14-4P 197374-16-6P 197374-17-7P 197374-18-8P
197374-19-9P 197374-20-2P 197374-21-3P 197374-22-4P 197374-29-1P
197374-30-4P 197374-31-5P 197374-32-6P 197374-34-8P 197374-37-1P
197374-38-2P 197374-39-3P 197374-41-7P 197374-42-8P 197374-43-9P
197374-44-0P 197374-45-1P 197374-48-4P 197374-49-5P 197374-50-8P
197374-51-9P 197374-52-0P 197374-53-1P 197374-54-2P 197374-55-3P
197374-56-4P 197374-57-5P 197374-58-6P **197374-59-7P**
197374-60-0P 197374-62-2P 197374-63-3P 197374-65-5P 197374-66-6P
197374-67-7P 197374-68-8P 197374-69-9P 197374-72-4P 197374-73-5P
197374-74-6P 197374-75-7P 197374-76-8P 197374-77-9P 197374-78-0P
197374-79-1P 197374-80-4P 197374-81-5P 197374-82-6P 197374-83-7P
197374-85-9P 197374-86-0P 197374-87-1P 197374-88-2P 197374-89-3P
197374-90-6P 197374-93-9P 197374-94-0P 197374-95-1P 197374-96-2P
197374-97-3P 197374-98-4P 197374-99-5P 197375-00-1P 197375-01-2P
197375-02-3P 197375-03-4P 197375-04-5P 197375-05-6P 197375-06-7P
197375-07-8P 197375-08-9P 197375-09-0P 197375-10-3P 197375-11-4P
197375-12-5P 197375-13-6P 197375-14-7P 197375-15-8P 197375-16-9P
197375-17-0P 197375-20-5P 197375-21-6P 197375-22-7P 197375-23-8P
197375-24-9P 197375-25-0P 197375-26-1P 197375-28-3P 197375-30-7P
197375-32-9P 197375-34-1P 197375-36-3P 197375-39-6P 197375-42-1P
197375-44-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors)

IT 197375-52-3P 197375-57-8P 197375-60-3P 197375-63-6P 197375-66-9P
197375-68-1P 197375-74-9P 197375-75-0P 197375-80-7P 197375-84-1P
197375-86-3P 197375-89-6P 197375-93-2P 197375-94-3P
197375-96-5P 197376-00-4P 197376-06-0P 197376-07-1P
197376-08-2P 197376-09-3P 197376-10-6P 197376-11-7P 197376-12-8P
197376-13-9P 197376-14-0P 197376-15-1P 197376-17-3P 197376-18-4P
197376-19-5P 197376-20-8P 197376-21-9P 197376-22-0P 197376-25-3P
197376-27-5P 197376-29-7P 197376-31-1P 197376-32-2P 197376-34-4P
197376-36-6P 197376-38-8P 197376-46-8P 197376-49-1P 197376-52-6P
197376-55-9P 197376-58-2P 197376-61-7P 197376-64-0P
197376-67-3P 197376-69-5P 197376-73-1P 197376-74-2P 197376-75-3P
197376-76-4P 197376-77-5P 197376-80-0P 197376-81-1P 197376-82-2P
197376-83-3P 197376-84-4P 197376-85-5P 197376-86-6P 197376-89-9P
197376-90-2P 197376-92-4P 197376-94-6P 197376-95-7P 197376-97-9P
197376-99-1P 197377-02-9P 197377-03-0P 197377-05-2P 197377-09-6P
197377-10-9P 197377-11-0P 197377-12-1P 197377-14-3P 197377-16-5P
197377-17-6P 197377-18-7P 197377-19-8P 197377-20-1P 197377-21-2P
197377-23-4P 197377-24-5P 197377-25-6P 197377-26-7P 197377-27-8P
197377-28-9P 197377-29-0P 197377-30-3P 197377-32-5P 197377-33-6P
197377-34-7P 197377-35-8P 197377-36-9P 197377-37-0P 197377-38-1P
197377-39-2P 197377-40-5P 197377-42-7P 197377-43-8P 197377-45-0P
197377-46-1P 197377-47-2P 197377-48-3P 197377-49-4P 197377-50-7P

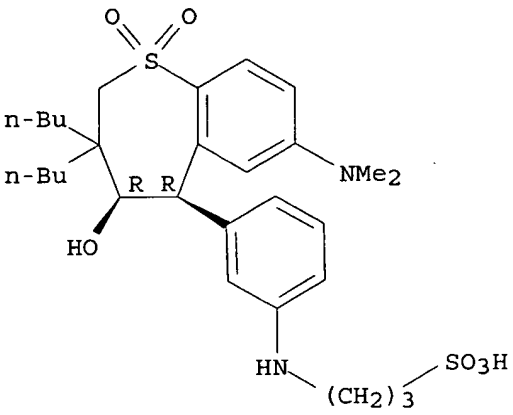
197377-51-8P 197377-52-9P 197377-53-0P 197377-54-1P 197377-55-2P
197377-58-5P 197377-60-9P 197377-61-0P 197377-62-1P 197377-63-2P
197377-64-3P 197377-65-4P 197377-66-5P 197377-68-7P 197377-69-8P
197377-70-1P 197377-71-2P 197377-72-3P 197377-73-4P 197377-74-5P
197377-75-6P 197377-76-7P 197377-77-8P 197377-78-9P 197377-79-0P
197377-82-5P 197377-83-6P 197377-84-7P 197377-85-8P 197377-86-9P
197377-90-5P 197377-91-6P 197377-93-8P 197377-94-9P 197377-96-1P
197377-98-3P **197384-36-4P** 197384-39-7P 197390-49-1P
197390-68-4P 213312-50-6P 213312-51-7P 213312-52-8P 213312-53-9P
213312-55-1P 213312-63-1P 213312-67-5P 213312-77-7P 213312-80-2P
213312-81-3P 213312-82-4P 213312-83-5P **213312-84-6P**
213312-86-8P 213312-87-9P 213312-89-1P 213312-90-4P 213312-92-6P
213312-93-7P 213312-94-8P 213312-95-9P 213312-96-0P 213312-97-1P
213312-98-2P 213312-99-3P 213313-00-9P 213313-01-0P 213313-02-1P
213313-03-2P 213313-05-4P 213313-06-5P 213313-07-6P 213313-08-7P
213313-10-1P 213313-11-2P 213313-15-6P 213313-18-9P 213313-19-0P
213313-20-3P 213313-21-4P 213313-22-5P 213313-23-6P
213313-24-7P 213313-25-8P 213313-26-9P 213313-27-0P 213313-28-1P
213313-29-2P 213313-30-5P 213313-31-6P 213313-32-7P 213313-33-8P
213313-34-9P 213313-35-0P 213386-72-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors)

IT 459-46-1P 1515-89-5P 3670-91-5P 24632-01-7P 70132-87-5P
120454-34-4P 120936-00-7P 123501-25-7P 178678-21-2P 178678-55-2P
178678-57-4P 178678-58-5P 178678-59-6P 178678-61-0P 178678-62-1P
178678-64-3P 178678-66-5P 178678-69-8P 178678-70-1P 178678-71-2P
178678-72-3P 178678-73-4P 197373-04-9P 197373-05-0P 197373-42-5P
197373-43-6P 197373-44-7P 197373-46-9P 197373-47-0P 197373-49-2P
197373-50-5P 197373-51-6P 197373-55-0P 197373-56-1P
197373-57-2P 197373-58-3P 197378-05-5P 197378-07-7P 197378-20-4P
197378-22-6P 197378-24-8P 197378-26-0P 197378-29-3P 197378-31-7P
197378-32-8P 197378-34-0P 197378-36-2P 197378-38-4P 197378-40-8P
197378-42-0P 197378-44-2P 197378-46-4P 197378-50-0P 197378-52-2P
197378-54-4P 197378-56-6P 197378-58-8P 213312-68-6P 213312-69-7P
213312-70-0P 213312-72-2P 213312-73-3P **213312-74-4P**
213312-76-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors)

IT **197373-37-8P 197374-04-2P 197374-59-7P**
197375-96-5P 197376-55-9P 197384-36-4P
213312-84-6P 213313-20-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors)

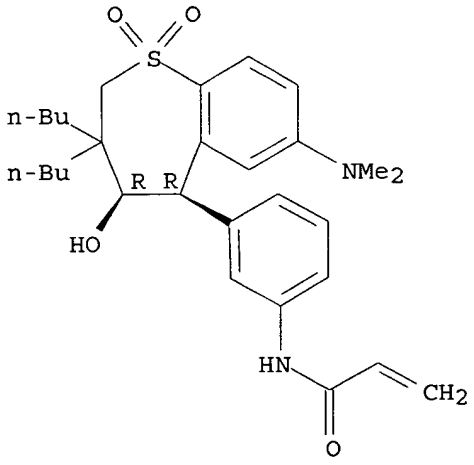
RN 197373-37-8 HCAPLUS
CN 1-Propanesulfonic acid, 3-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



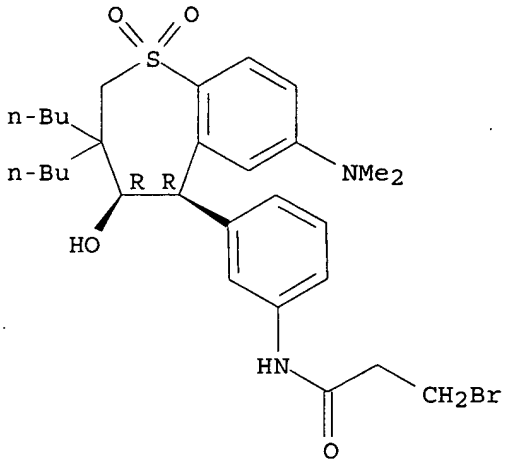
RN 197374-04-2 HCAPLUS
CN 2-Propenamide, N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



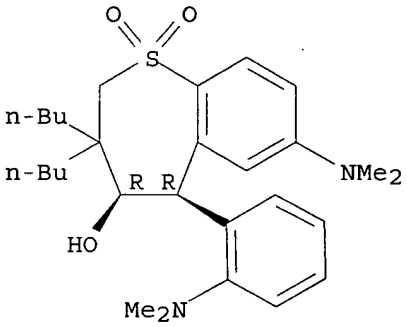
RN 197374-59-7 HCAPLUS
CN Propanamide, 3-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



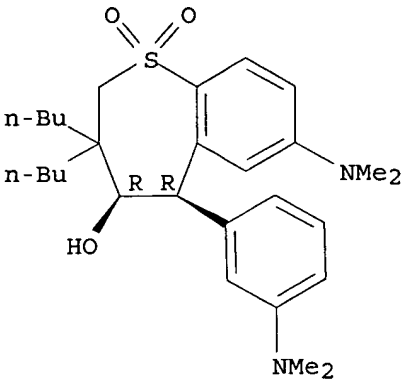
RN 197375-96-5 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[2-(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 197376-55-9 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[3-(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

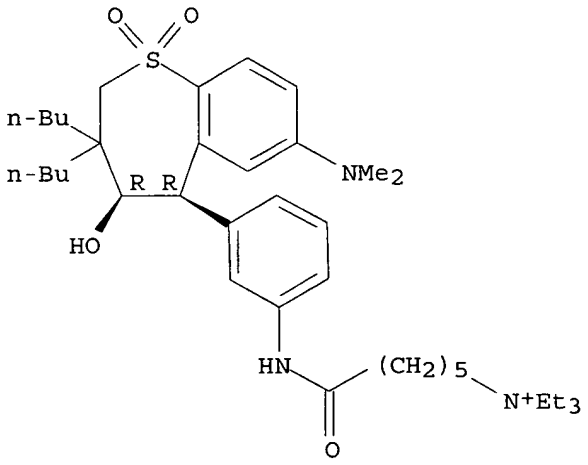


RN 197384-36-4 HCAPLUS
CN 1-Hexanaminium, 6-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-6-oxo-, rel-, salt with trifluoroacetic acid (1:1) (9CI) (CA INDEX NAME)

CM 1

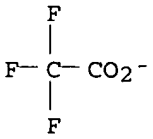
CRN 197384-35-3
CMF C38 H62 N3 O4 S

Relative stereochemistry.



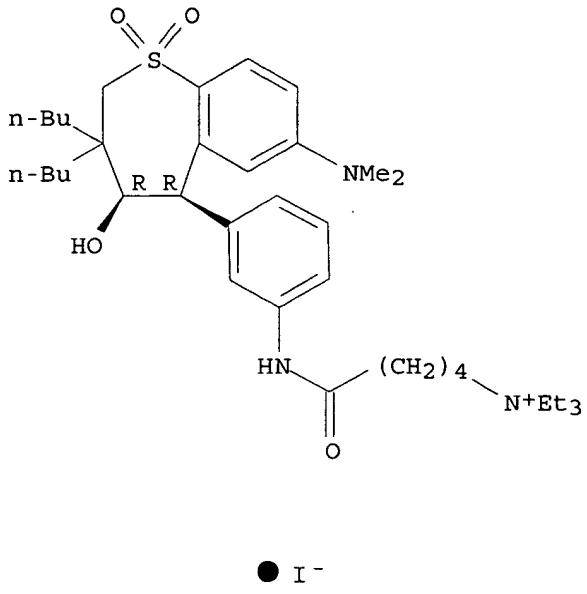
CM 2

CRN 14477-72-6
CMF C2 F3 O2



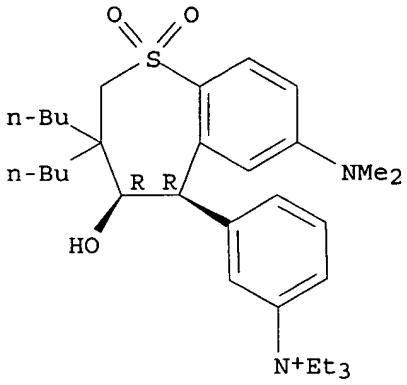
RN 213312-84-6 HCAPLUS
CN 1-Pentanaminium, 5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-oxo-, iodide, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 213313-20-3 HCAPLUS
CN Benzenaminium, 3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]-N,N,N-triethyl-, bromide, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

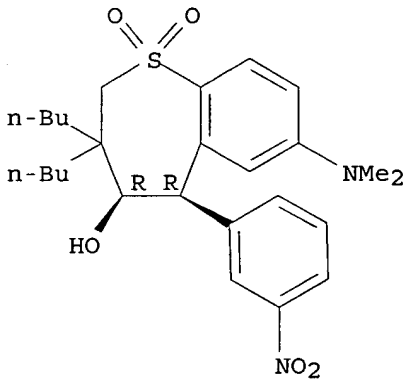


● Br^-

IT **197373-50-5P 197373-51-6P 213312-74-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors)

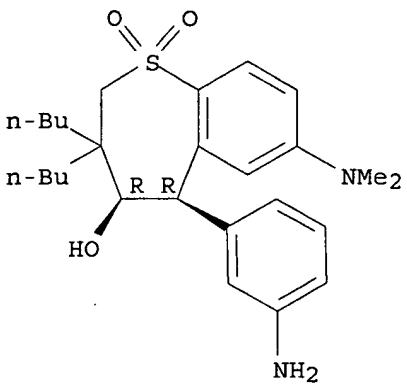
RN 197373-50-5 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



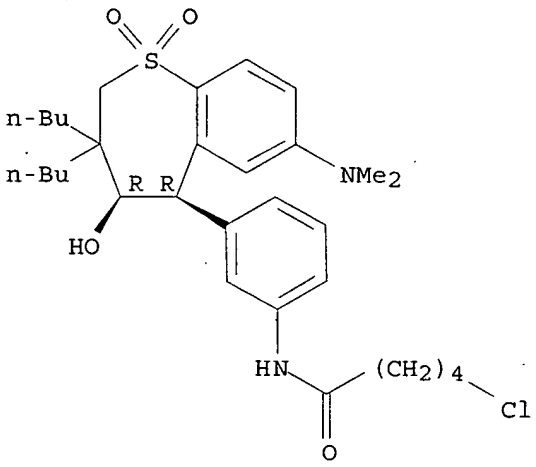
RN 197373-51-6 HCAPLUS
CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 213312-74-4 HCAPLUS
CN Pentanamide, 5-chloro-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L9 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:623163 HCAPLUS
DOCUMENT NUMBER: 127:307312
TITLE: Novel benzothiepines having activity as inhibitors of ileal bile acid transport and taurocholate uptake
INVENTOR(S): Reitz, David B.; Lee, Len F.; Li, Jinglin J.; Huang, Horng-Chih; Tremont, Samuel J.; Miller, Raymond E.; Banerjee, Shyamal C.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA; Reitz, David B.; Lee, Len F.; Li, Jinglin J.; Huang, Horng-Chih; Tremont, Samuel J.; Miller, Raymond E.; Banerjee, Shyamal C.
SOURCE: PCT Int. Appl., 406 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9

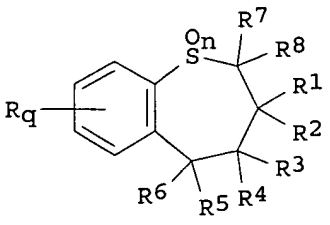
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9733882	A1	19970918	WO 1997-US4076	19970311
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2248586	AA	19970918	CA 1997-2248586	19970311
CA 2506703	AA	19970918	CA 1997-2506703	19970311
AU 9723266	A1	19971001	AU 1997-23266	19970311
AU 723123	B2	20000817		
EP 888333	A1	19990107	EP 1997-915976	19970311
EP 888333	B1	20050831		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
CN 1221414	A	19990630	CN 1997-194503	19970311
CN 1110494	B	20030604		
BR 9708042	A	19990727	BR 1997-8042	19970311
JP 2001526627	T2	20011218	JP 1997-532875	19970311
RU 2202549	C2	20030420	RU 1998-118643	19970311
CN 1515567	A	20040728	CN 2003-2003110500	19970311
EP 1440972	A1	20040728	EP 2004-10088	19970311
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
AT 303378	E	20050915	AT 1997-915976	19970311
NO 9804146	A	19981030	NO 1998-4146	19980909
AU 761249	B2	20030529	AU 2000-53394	20000816
US 2003171426	A1	20030911	US 2002-76091	20020215
US 6642268	B2	20031104		

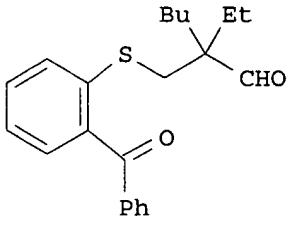
PRIORITY APPLN. INFO.:	US 1996-13119P	P	19960311
	US 1997-816065	A	19970311
	US 1994-305526	B2	19940913
	US 1995-517051	B1	19950821
	AU 1997-23266	A3	19970311
	CA 1997-2248586	A3	19970311
	EP 1997-915976	A3	19970311
	US 1997-40660P	P	19970311
	WO 1997-US4076	W	19970311
	US 1997-831284	B3	19970331
	US 2000-676466	A3	20000929

OTHER SOURCE(S): MARPAT 127:307312

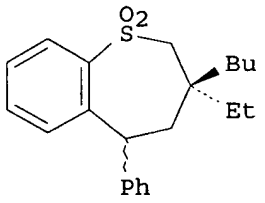
GI



I



II



III

AB Novel benzothiepines I [q = 1-4; n = 0-2; R = H, halo, (un)substituted alk(en/yn)yl, acyloxy, aryl, heterocyclyl, OH or NH2 or SH or derivs., etc.; R1, R2 = H, (un)substituted and/or heteroatom-replaced alk(en/yn)yl, cycloalkyl, aryl, alkoxy, alkylthio, dialkylamino; or CR1R2 = C3-10 cycloalkylidene; R3, R4 = H, alk(en/yn)yl, acyloxy, aryl, heterocyclyl, OH or NH2 or SH or derivs.; or R3R4 = O, S, NH, NOH, NNH2, CH2 or derivs.; R5, R6 = H, (un)substituted alk(en/yn)yl, cycloalkyl, aryl, heterocyclyl, OH or SH or derivs.; R7, R8 = H, alkyl] and their derivs. and analogs are provided. Also provided are pharmaceutical compns. containing I and methods of their medical use, particularly in the prophylaxis and treatment of hyperlipidemic conditions, such as those associated with atherosclerosis or hypercholesterolemia. For instance, the keto aldehyde II was cyclized by Zn/TiCl3, and the resultant cycloolefin was oxidized and epoxidized by m-ClC6H4C(O)OOH and hydrogenated over Pd/C to give epimeric title compds. α- and β-III in 25% and 13% yield, plus addnl. compds. In a test for inhibition of IBAT-mediated uptake of [14C]-taurocholate in H14 cells in vitro, β-III had an IC50 of 5 μM.

IC ICM C07D337-08
ICS C07D409-10; C08G065-329; A61K031-38

CC 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

IT 178678-22-3P 178678-23-4P 178678-24-5P 178678-25-6P 178678-26-7P
178678-27-8P 178678-29-0P 178678-34-7P 178678-37-0P 178678-46-1P
178678-49-4P 178678-50-7P 178678-51-8P 178897-97-7P 178897-98-8P
178898-00-5P 197372-71-7P 197372-76-2P 197372-77-3P 197372-78-4P
197372-97-7P 197373-13-0P 197373-14-1P 197373-42-5P 197373-44-7P
197373-46-9P 197373-47-0P 197373-49-2P **197373-50-5P**
197373-51-6P **197373-52-7P** 197373-55-0P 197373-56-1P
197373-57-2P 197373-58-3P 197375-48-7P 197375-49-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of benzothiepines as antihyperlipidemics)

IT 178678-28-9P 178678-30-3P 178678-31-4P 178678-33-6P 178678-35-8P
178678-36-9P 178678-38-1P 178678-39-2P 178678-40-5P 178678-41-6P
178678-42-7P 178678-43-8P 178678-44-9P 178678-45-0P 178678-47-2P
178678-48-3P 178678-52-9P 178678-53-0P 178678-54-1P 178897-95-5P

178897-96-6P 178897-99-9P 178898-01-6P 178898-02-7P 178898-03-8P
178898-04-9P 178898-05-0P 197372-64-8P 197372-65-9P 197372-66-0P
197372-67-1P 197372-68-2P 197372-69-3P 197372-70-6P 197372-72-8P
197372-73-9P 197372-74-0P 197372-75-1P 197372-79-5P 197372-80-8P
197372-81-9P 197372-82-0P 197372-83-1P 197372-84-2P 197372-85-3P
197372-86-4P 197372-87-5P 197372-88-6P 197372-89-7P 197372-90-0P
197372-91-1P 197372-92-2P 197372-93-3P 197372-94-4P 197372-95-5P
197372-96-6P 197372-98-8P 197372-99-9P 197373-00-5P 197373-01-6P
197373-02-7P 197373-03-8P 197373-04-9P 197373-05-0P 197373-06-1P
197373-07-2P 197373-08-3P 197373-09-4P 197373-10-7P 197373-11-8P
197373-12-9P 197373-15-2P 197373-16-3P 197373-17-4P 197373-18-5P
197373-19-6P 197373-20-9P 197373-22-1P 197373-24-3P 197373-25-4P
197373-26-5P 197373-27-6P 197373-28-7P 197373-29-8P 197373-30-1P
197373-31-2P 197373-32-3P 197373-33-4P 197373-34-5P 197373-35-6P
197373-36-7P **197373-37-8P** 197373-38-9P 197373-39-0P
197373-40-3P 197373-41-4P 197373-43-6P 197373-45-8P 197373-48-1P
197373-54-9P 197373-59-4P 197373-60-7P 197373-61-8P
197373-62-9P 197373-63-0P 197373-64-1P 197373-66-3P 197373-67-4P
197373-68-5P 197373-69-6P 197373-70-9P 197373-71-0P 197373-72-1P
197373-73-2P 197373-75-4P 197373-76-5P 197373-77-6P 197373-78-7P
197373-79-8P 197373-80-1P 197373-81-2P 197373-83-4P 197373-85-6P
197373-87-8P 197373-90-3P 197373-93-6P 197373-95-8P 197373-97-0P
197373-99-2P 197374-00-8P 197374-01-9P 197374-02-0P 197374-03-1P
197374-04-2P 197374-06-4P 197374-08-6P 197374-09-7P
197374-10-0P 197374-11-1P 197374-13-3P 197374-14-4P 197374-16-6P
197374-17-7P 197374-18-8P 197374-19-9P 197374-20-2P 197374-21-3P
197374-22-4P 197374-23-5P 197374-24-6P 197374-25-7P 197374-26-8P
197374-27-9P 197374-28-0P 197374-29-1P 197374-30-4P 197374-31-5P
197374-32-6P 197374-34-8P 197374-35-9P 197374-36-0P 197374-37-1P
197374-38-2P 197374-39-3P 197374-40-6P 197374-41-7P 197374-42-8P
197374-43-9P 197374-44-0P 197374-45-1P 197374-46-2P 197374-47-3P
197374-48-4P 197374-49-5P 197374-50-8P 197374-51-9P 197374-52-0P
197374-53-1P 197374-54-2P 197374-55-3P 197374-56-4P 197374-57-5P
197374-58-6P **197374-59-7P** 197374-60-0P 197374-62-2P
197374-63-3P 197374-64-4P 197374-65-5P 197374-66-6P 197374-67-7P
197374-68-8P 197374-69-9P 197374-71-3P 197374-72-4P 197374-73-5P
197374-74-6P 197374-75-7P 197374-76-8P 197374-77-9P 197374-78-0P
197374-79-1P 197374-80-4P 197374-81-5P 197374-82-6P 197374-83-7P
197374-84-8P 197374-85-9P 197374-86-0P 197374-87-1P 197374-88-2P
197374-89-3P 197374-90-6P 197374-91-7P 197374-92-8P 197374-93-9P
197374-94-0P 197374-95-1P 197374-96-2P 197374-97-3P 197374-98-4P
197374-99-5P 197375-00-1P 197375-01-2P 197375-02-3P 197375-03-4P
197375-04-5P 197375-05-6P 197375-06-7P 197375-07-8P 197375-08-9P
197375-09-0P 197375-10-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzothiepines as antihyperlipidemics)

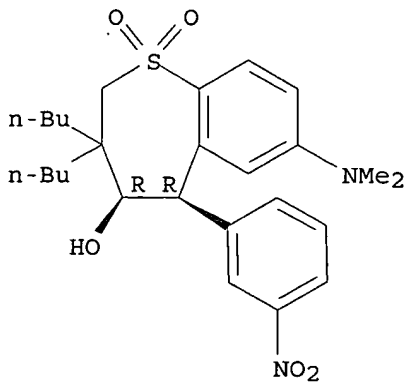
IT 197375-11-4P 197375-12-5P 197375-13-6P 197375-14-7P 197375-15-8P
197375-16-9P 197375-17-0P 197375-20-5P 197375-21-6P 197375-22-7P
197375-23-8P 197375-24-9P 197375-25-0P 197375-26-1P 197375-28-3P
197375-30-7P 197375-32-9P 197375-34-1P 197375-36-3P 197375-39-6P
197375-42-1P 197375-44-3P 197375-52-3P 197375-57-8P 197375-60-3P
197375-63-6P 197375-66-9P 197375-68-1P 197375-70-5P 197375-72-7P
197375-74-9P 197375-75-0P 197375-76-1P 197375-80-7P 197375-82-9P
197375-84-1P 197375-86-3P 197375-87-4P 197375-89-6P 197375-91-0P
197375-93-2P 197375-94-3P **197375-96-5P** 197375-98-7P
197376-00-4P 197376-02-6P 197376-04-8P 197376-06-0P 197376-07-1P
197376-08-2P 197376-09-3P 197376-10-6P 197376-11-7P 197376-12-8P

197376-13-9P 197376-14-0P 197376-15-1P 197376-16-2P 197376-17-3P
197376-18-4P 197376-19-5P 197376-20-8P 197376-21-9P 197376-22-0P
197376-25-3P 197376-27-5P 197376-29-7P 197376-31-1P 197376-32-2P
197376-34-4P 197376-36-6P 197376-38-8P 197376-40-2P
197376-42-4P 197376-46-8P 197376-49-1P 197376-52-6P
197376-55-9P 197376-58-2P 197376-61-7P 197376-64-0P
197376-67-3P 197376-69-5P 197376-73-1P 197376-74-2P 197376-75-3P
197376-76-4P 197376-77-5P 197376-78-6P 197376-79-7P 197376-80-0P
197376-81-1P 197376-82-2P 197376-83-3P 197376-84-4P 197376-85-5P
197376-86-6P 197376-88-8P 197376-89-9P 197376-90-2P 197376-92-4P
197376-94-6P 197376-95-7P 197376-97-9P 197376-99-1P 197377-00-7P
197377-02-9P 197377-03-0P 197377-05-2P 197377-09-6P 197377-10-9P
197377-11-0P 197377-12-1P 197377-14-3P 197377-16-5P 197377-17-6P
197377-18-7P 197377-19-8P 197377-20-1P 197377-21-2P 197377-22-3P
197377-23-4P 197377-24-5P 197377-25-6P 197377-26-7P 197377-27-8P
197377-28-9P 197377-29-0P 197377-30-3P 197377-31-4P 197377-32-5P
197377-33-6P 197377-34-7P 197377-35-8P 197377-36-9P 197377-37-0P
197377-38-1P 197377-39-2P 197377-40-5P 197377-42-7P 197377-43-8P
197377-45-0P 197377-46-1P 197377-47-2P 197377-48-3P 197377-49-4P
197377-50-7P 197377-51-8P 197377-52-9P 197377-53-0P 197377-54-1P
197377-55-2P 197377-57-4P 197377-58-5P 197377-60-9P 197377-61-0P
197377-62-1P 197377-63-2P 197377-64-3P 197377-65-4P 197377-66-5P
197377-67-6P 197377-68-7P 197377-69-8P 197377-70-1P 197377-71-2P
197377-72-3P 197377-73-4P 197377-74-5P 197377-75-6P 197377-76-7P
197377-77-8P 197377-78-9P 197377-79-0P 197377-81-4P 197377-82-5P
197377-83-6P 197377-84-7P 197377-85-8P 197377-86-9P 197377-90-5P
197377-91-6P 197377-93-8P 197377-94-9P 197377-96-1P 197377-98-3P
197384-36-4P 197384-39-7P 197390-49-1P 197390-68-4P
213386-72-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzothiepines as antihyperlipidemics)

IT **197373-50-5P 197373-51-6P 197373-52-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of benzothiepines as antihyperlipidemics)

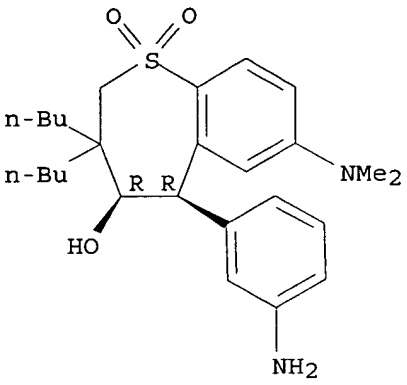
RN 197373-50-5 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



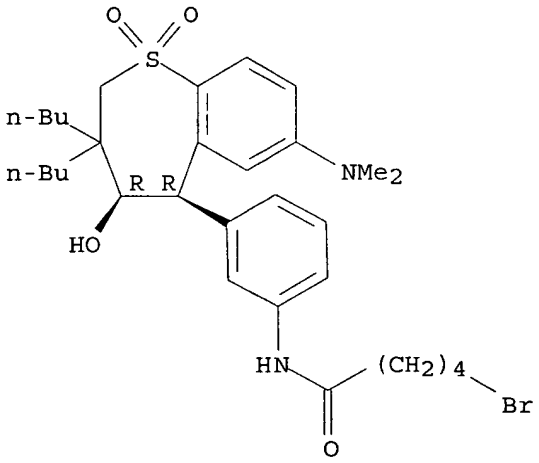
RN 197373-51-6 HCAPLUS
CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



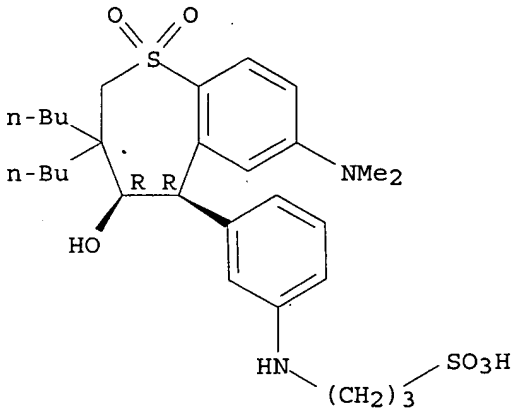
RN 197373-52-7 HCAPLUS
CN Pentanamide, 5-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



IT **197373-37-8P 197373-54-9P 197374-04-2P**
197374-59-7P 197375-96-5P 197376-42-4P
197376-55-9P 197384-36-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzothiepines as antihyperlipidemics)
RN 197373-37-8 HCAPLUS
CN 1-Propanesulfonic acid, 3-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

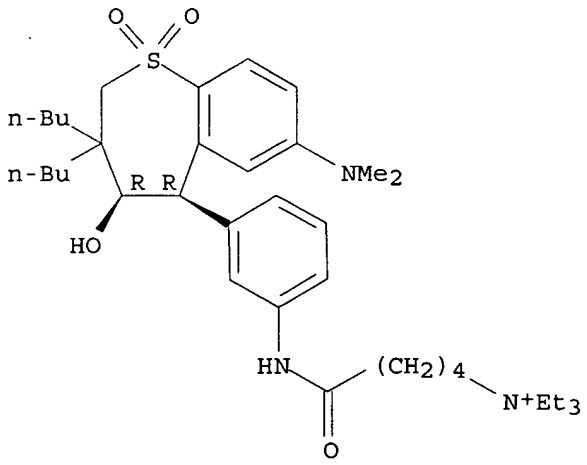


RN 197373-54-9 HCAPLUS
CN 1-Pentanaminium, 5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-oxo-, rel-, salt with trifluoroacetic acid (1:1) (9CI) (CA INDEX NAME)

CM 1

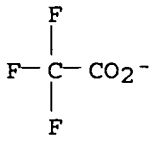
CRN 197373-53-8
CMF C37 H60 N3 O4 S

Relative stereochemistry.



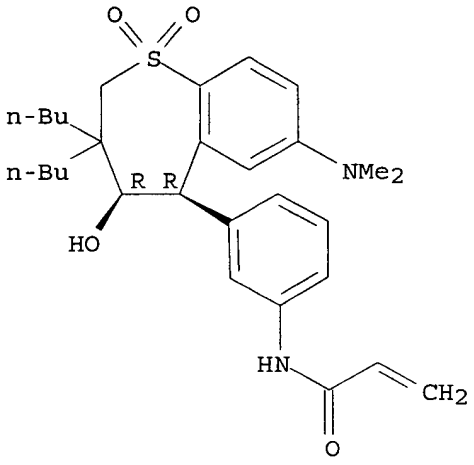
CM 2

CRN 14477-72-6
CMF C2 F3 O2



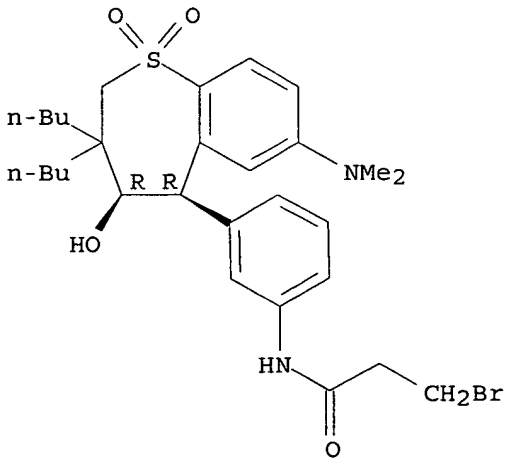
RN 197374-04-2 HCAPLUS
CN 2-Propenamide, N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



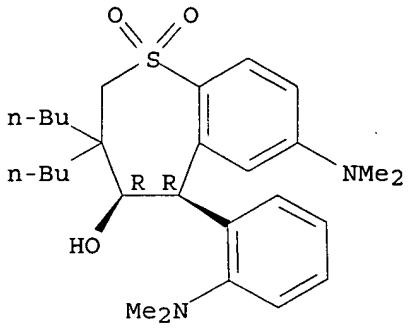
RN 197374-59-7 HCAPLUS
CN Propanamide, 3-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



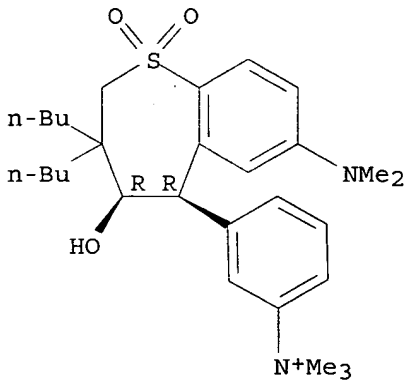
RN 197375-96-5 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[2-(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 197376-42-4 HCAPLUS
CN Benzenaminium, 3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]-N,N,N-trimethyl-, iodide, rel- (9CI) (CA INDEX NAME)

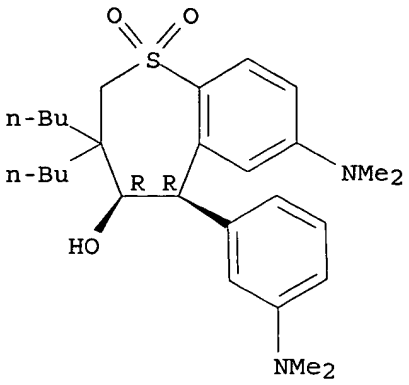
Relative stereochemistry.



● I⁻

RN 197376-55-9 HCAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[3-(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

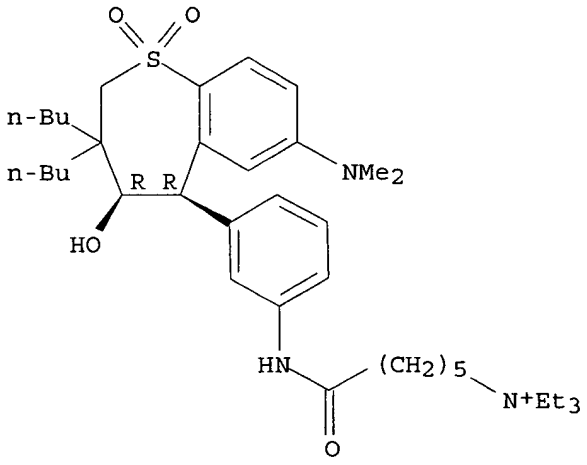


RN 197384-36-4 HCAPLUS
CN 1-Hexanaminium, 6-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-6-oxo-, rel-, salt with trifluoroacetic acid (1:1) (9CI) (CA INDEX NAME)

CM 1

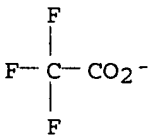
CRN 197384-35-3
CMF C38 H62 N3 O4 S

Relative stereochemistry.



CM 2

CRN 14477-72-6
CMF C2 F3 O2



```
=> fil hcap medline embase biosis
FILE 'HCAPLUS' ENTERED AT 17:07:30 ON 05 SEP 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'MEDLINE' ENTERED AT 17:07:30 ON 05 SEP 2006

FILE 'EMBASE' ENTERED AT 17:07:30 ON 05 SEP 2006
Copyright (c) 2006 Elsevier B.V. All rights reserved.

FILE 'BIOSIS' ENTERED AT 17:07:30 ON 05 SEP 2006
Copyright (c) 2006 The Thomson Corporation

=> d l26 ibib abs tot

L26  ANSWER 1 OF 65  HCAPLUS  COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2005:144437  HCAPLUS
DOCUMENT NUMBER:          142:233695
TITLE:                    Heterologous expression of human
                          α6β4β3α5 nicotinic acetylcholine
                          receptors: binding properties consistent with their
                          natural expression require quaternary subunit assembly
                          including the α5 subunit
AUTHOR(S):                Grinevich, Vladimir P.; Letchworth, Sharon R.;
                          Lindenberger, Kari A.; Menager, Jean; Mary, Veronique;
                          Sadieva, Khalima A.; Buhlman, Lori M.; Bohme, Georg
                          Andrees; Pradier, Laurent; Benavides,
                          Jesus; Lukas, Ronald J.; Bencherif, Merouane
CORPORATE SOURCE:         Targacept, Inc., Winston-Salem, NC, USA
SOURCE:                   Journal of Pharmacology and Experimental Therapeutics
                          (2005), 312(2), 619-626
                          CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER:                American Society for Pharmacology and Experimental
                          Therapeutics
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Heterologous expression and lesioning studies were conducted to identify
     possible subunit assembly partners in nicotinic acetylcholine receptors
     (nAChR) containing α6 subunits (α6* nAChR).  SHEP1 human
     epithelial cells were transfected with the requisite subunits to achieve
     stable expression of human α6β2, α6β4,
     α6β2β3, α6β4β3, or
     α6β4β3α5 nAChR.  Cells expressing subunits needed to
     form α6β4β3α5 nAChR exhibited saturable
     [3H]epibatidine binding (Kd = 95.9 pM and Bmax = 84.5 fmol/mg of protein).
     The rank order of binding competition potency (Ki) for prototypical
     nicotinic compds. was α-conotoxin MII (6 nM) > nicotine (156 nM)
     .apprx. methyllycaconitine (200 nM) > α-bungarotoxin (>10 μM),
     similar to that for nAChR in dopamine neurons displaying a distinctive
```

pharmacol. 6-Hydroxydopamine lesioning studies indicated that β3 and α5 subunits are likely partners of the α6 subunits in nAChR expressed in dopaminergic cell bodies. Similar to findings in rodents, quant. real-time reverse transcription-polymerase chain reactions of human brain indicated that α6 subunit mRNA expression was 13-fold higher in the substantia nigra than in the cortex or the rest of the brain. Thus, heterologous expression studies suggest that the human α5 subunit makes a critical contribution to α6β4β3α5 nAChR assembly into a ligand-binding form with native α6*-nAChR-like pharmacol. and of potential physiol. and pathophysiol. relevance.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 2 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2005:47732 HCAPLUS
DOCUMENT NUMBER: 143:76040
TITLE: ABCA2 is a strong genetic risk factor for early-onset Alzheimer's disease
AUTHOR(S): Mace, Sandrine; Cousin, Emmanuelle; Ricard, Sylvain; Genin, Emmanuelle; Spanakis, Emmanuel; Lafargue-Soubigou, Carole; Genin, Berengere; Fournel, Raphael; Roche, Sandrine; Haussy, Gilles; Massey, Florence; Soubigou, Stephane; Brefort, Georges; Benoit, Patrick; Brice, Alexis; Campion, Dominique; Hollis, Melvyn; **Pradier, Laurent**; **Benavides, Jesus**; Deleuze, Jean-Francois
CORPORATE SOURCE: Aventis Pharma, Evry Genetics Center and Neurodegenerative Disease Group, Paris Research Center, Vitry-sur-Seine, 94400, Fr.
SOURCE: Neurobiology of Disease (2005), 18(1), 119-125
CODEN: NUDIEM; ISSN: 0969-9961
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent epidemiol., biol. and genetic data indicate a relationship between cholesterol and Alzheimer's disease (AD) including the association of polymorphisms of ABCA1 (a gene that is known to participate in cholesterol and phospholipid transport) with AD prevalence. Based on these data, we postulated that genetic variation in the related and brain-specific ABCA2 gene leads to increase risk of AD. A large case-control study was conducted where the sample was randomly divided into a hypothesis-testing sample (230 cases/286 controls) and a validation sample (210 cases/233 controls). Among the 45 SNPs we tested, one synonymous SNP (rs908832) was found significantly associated with AD in both samples. Addnl. analyses performed on the whole sample showed a very strong association between this marker and early-onset AD (OR = 3.82, 95% C.I. = [2.00 - 7.30], P = 5 + 10-5). Further research is needed to understand the functional role of this polymorphism. However, together with the reported assocns. of AD with APOE, CYP46A1 and ABCA1, the present result adds a very significant support for the role of cholesterol and phospholipid homeostasis in AD and a rationale for testing novel cholesterol homeostasis-related therapeutic strategies in AD.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 3 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2005:978141 HCAPLUS
DOCUMENT NUMBER: 144:168853
TITLE: Unraveling substantia nigra sequential gene expression

in a progressive MPTP-lesioned macaque model of Parkinson's disease
AUTHOR(S): Bassilana, F.; Mace, N.; Li, Q.; Stutzmann, J. M.; Gross, C. E.; **Pradier, L.**; **Benavides, J.**; Menager, J.; Bezard, E.
CORPORATE SOURCE: Sanofi-Aventis, Vitry sur Seine, Fr.
SOURCE: Neurobiology of Disease (2005), 20(1), 93-103
CODEN: NUDIEM; ISSN: 0969-9961
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Taking advantage of a progressive nonhuman primate model mimicking Parkinson's disease (PD) evolution, we monitored transcriptional fluctuations in the substantia nigra using Affymetrix microarrays in control (normal), saline-treated (normal), 6 days-treated (asymptomatic with 20% cell loss), 12 days-treated (asymptomatic with 40% cell loss) and 25 days-treated animals (fully parkinsonian with 85% cell loss). Two statistical methods were used to ascertain the regulation and real-time quant. PCR was used to confirm their regulation. Surprisingly, the number of deregulated transcripts is limited at all time points and five clusters exhibiting different profiles were defined using a hierarchical clustering algorithm. Such profiles are likely to represent activation/deactivation of mechanisms of different nature. We briefly speculate about (i) the existence of yet unknown compensatory mechanisms is unraveled, (ii) the putative triggering of a developmental program in the mature brain in reaction to progressing degeneration and finally, (iii) the activation of mechanisms leading eventually to death in final stage. These data should help development of new therapeutic approaches either aimed at enhancing existing compensatory mechanisms or at protecting dopamine neurons.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 4 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2004:1010181 HCAPLUS
DOCUMENT NUMBER: 142:21640
TITLE: Amyloid β-induced Changes in Nitric Oxide Production and Mitochondrial Activity Lead to Apoptosis
AUTHOR(S): Keil, Uta; Bonert, Astrid; Marques, Celio A.; Scherping, Isabel; Weyermann, Joerg; Strosznajder, Joanna B.; Mueller-Spahn, Franz; Haass, Christian; Czech, Christian; **Pradier, Laurent**; Mueller, Walter E.; Eckert, Anne
CORPORATE SOURCE: Departments of Pharmacology, Biocenter, University of Frankfurt, Frankfurt, 60439, Germany
SOURCE: Journal of Biological Chemistry (2004), 279(48), 50310-50320
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Increasing evidence suggests an important role of mitochondrial dysfunction in the pathogenesis of Alzheimer's disease. Thus, the authors investigated the effects of acute and chronic exposure to increasing concns. of amyloid β (Aβ) on mitochondrial function and nitric oxide (NO) production in vitro and in vivo. The authors' data demonstrate that PC12 cells and human embryonic kidney cells bearing the Swedish double mutation in the amyloid precursor protein gene (APPsw), exhibiting

substantial Aβ levels, have increased NO levels and reduced ATP levels. The **inhibition** of intracellular Aβ production by a functional γ- **secretase inhibitor** normalizes NO and ATP levels, indicating a direct involvement of Aβ in these processes. Extracellular treatment of PC12 cells with comparable Aβ concns. only leads to weak changes, demonstrating the important role of intracellular Aβ. In 3-mo-old **APP** transgenic (tg) mice, which exhibit no plaques but already detectable Aβ levels in the brain, reduced ATP levels can also be observed showing the in vivo relevance of the authors' findings. Moreover, the authors could demonstrate that **APP** is present in the mitochondria of APPsw PC12 cells. This presence might be directly involved in the impairment of cytochrome c oxidase activity and depletion of ATP levels in APPsw PC12 cells. In addition, APPsw human embryonic kidney cells, which produce 20-fold increased Aβ levels compared with APPsw PC12 cells, and **APP** tg mice already show a significantly decreased mitochondrial membrane potential under basal conditions. The authors suggest a hypothetical sequence of pathogenic steps linking mutant **APP** expression and amyloid production with enhanced NO production and mitochondrial dysfunction finally leading to cell death.

REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 5 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 2004:910579 HCAPLUS
DOCUMENT NUMBER: 142:4782
TITLE: Massive CA1/2 neuronal loss with intraneuronal and N-terminal truncated Aβ42 accumulation in a novel Alzheimer transgenic model
AUTHOR(S): Casas, Caty; Sergean, Nicolas; Itier, Jean-Michel; Blanchard, Veronique; Wirths, Oliver; van der Kolk, Nicolien; Vingtdeux, Valerie; van de Steeg, Evita; Ret, Gwenaelle; **Canton, Thierry**; Drobecq, Herve; Clark, Allan; Bonici, Bruno; Delacourte, Andre; **Benavides, Jesus**; Schmitz, Christoph; Tremp, Gunter; Bayer, Thomas A.; Benoit, Patrick; **Pradier, Laurent**
CORPORATE SOURCE: Departments of Central Nervous System/Alzheimer Disease, INSERM U422, Aventis-Pharma Paris Research Center, Paris, Fr.
SOURCE: American Journal of Pathology (2004), 165(4), 1289-1300
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Alzheimer's disease (AD) is characterized by a substantial degeneration of pyramidal neurons and the appearance of neuritic plaques and neurofibrillary tangles. Here we present a novel transgenic mouse model, APPSLPS1KI that closely mimics the development of AD-related neuropathol. features including a significant hippocampal neuronal loss. This transgenic mouse model carries M233T/L235P knocked-in mutations in presenilin-1 and overexpresses mutated human β-amyloid (Aβ) precursor protein. Aβx-42 is the major form of Aβ species present in this model with progressive development of a complex pattern of N-truncated variants and dimers, similar to those observed in AD brain. At 10 mo of age, an extensive neuronal loss (>50%) is present in the CA1/2 hippocampal pyramidal cell layer that correlates with strong accumulation of intraneuronal Aβ and thioflavine-S-pos. intracellular material but

not with extracellular Aβ deposits. A strong reactive astrogliosis develops together with the neuronal loss. This loss is already detectable at 6 mo of age and is PSIK1 gene dosage-dependent. Thus, APPSLPS1KI mice further confirm the critical role of intraneuronal Aβ42 in neuronal loss and provide an excellent tool to investigate therapeutic strategies designed to prevent AD neurodegeneration.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 6 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 6

ACCESSION NUMBER: 2004:984714 HCAPLUS

DOCUMENT NUMBER: 142:169848

TITLE: In vitro and in vivo characterization of TC-1827, a novel brain α4β2 nicotinic receptor agonist with pro-cognitive activity

AUTHOR(S): Bohme, Georg Andrees; Letchworth, Sharon R.; Piot-Grosjean, Odile; Gatto, Gregory J.; Obinu, Marie-Carmen; Caldwell, William S.; Laville, Michel; Brunel, Pascale; Pellerin, Rachel; Leconte, Jean-Pierre; Genevois-Borella, Arielle; Dubedat, Pierre; Mazadier, Martine; **Pradier, Laurent**; Bencherif, Merouane; **Benavides, Jesus**

CORPORATE SOURCE: Centre de Recherches de Paris, Aventis Pharma S.A., Vitry Sur Seine, Fr.

SOURCE: Drug Development Research (2004), 62(1), 26-40
CODEN: DDREDK; ISSN: 0272-4391

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Nicotine activates specific receptors that are cation-permeable ionic channels located in the central and autonomous nervous systems, as well as at the neuromuscular junction. Administration of nicotine to animals and humans has been shown to enhance cognitive processes. However, side effects linked to the activation of peripheral nicotinic receptors limit the usefulness of nicotine for the treatment of cognitive disorders such as Alzheimer's disease (AD) or mild cognitive impairments (MCI). The synthesis and properties of TC-1827, a novel metanicotine derivative that activates brain α4β2 nicotinic receptors is described. TC-1827 has high affinity for nicotine-labeled receptors in the cortex (Ki = 34 nM), full-agonist intrinsic activity in α4β2-mediated neurotransmitter release studies in synaptosomes, and has no functional activity at nicotinic receptors in ganglionic or muscular cell lines. The compound enhances long-term potentiation in hippocampal slices, a form of synaptic plasticity thought to be involved in information storage at the cellular level. In vivo studies demonstrate that TC-1827 dose-dependently occupies thalamic nicotinic receptors labeled with [3H]-cytisine, increases cortical extracellular acetylcholine levels following oral administration, and enhances cognitive performance in rat and mice behavioral procedures of learning and memory. Pharmacokinetic studies in mice, rats, and monkeys indicated that TC-1827 has good oral absorption with a first pass effect resulting in bioavailabilities of 13-65% across dose/species. Cardiovascular safety studies indicate good cardiovascular tolerability for this compound The present data demonstrate that TC-1827 is a selective and potent activator of brain α4β2 nicotinic receptors and is a prototypical member of a new class of compds. with potential utility in the symptomatic treatment of cognitive disorders including AD and MCI.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 7 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 2003:704890 HCAPLUS
DOCUMENT NUMBER: 139:321545
TITLE: Parkin gene inactivation alters behaviour and dopamine neurotransmission in the mouse
AUTHOR(S): Itier, Jean-Michel; Ibanez, Pablo; Mena, Maria Angeles; Abbas, Nacer; Cohen-Salmon, Charles; Bohme, Georg Andrees; Laville, Michel; Pratt, Jeremy; Corti, Olga; **Pradier, Laurent**; Ret, Gwenaeelle; Joubert, Chantal; Periquet, Magali; Araujo, Francisco; Negroni, Julia; Casarejos, Maria Jose; Canals, Santiago; Solano, Rosa; Serrano, Alba; Gallego, Eva; Sanchez, Marina; Denefle, Patrice; **Benavides, Jesus**; Tremp, Guenter; Rooney, Thomas A.; Brice, Alexis; Garcia de Yebenes, Justo
CORPORATE SOURCE: Functional Genomics Department, Aventis Pharma SA, Vitry-sur-Seine, F-94400, Fr.
SOURCE: Human Molecular Genetics (2003), 12(18), 2277-2291
CODEN: HMGEE5; ISSN: 0964-6906
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mutations of the parkin gene are the most frequent cause of early onset autosomal recessive parkinsonism (EO-AR). Here the authors show that inactivation of the parkin gene in mice results in motor and cognitive deficits, inhibition of amphetamine-induced dopamine release and inhibition of glutamate neurotransmission. The levels of dopamine are increased in the limbic brain areas of parkin mutant mice and there is a shift towards increased metabolism of dopamine by MAO. Although there was no evidence for a reduction of nigrostriatal dopamine neurons in the parkin mutant mice, the level of dopamine transporter protein was reduced in these animals, suggesting a decreased d. of dopamine terminals, or adaptative changes in the nigrostriatal dopamine system. GSH levels were increased in the striatum and fetal mesencephalic neurons from parkin mutant mice, suggesting that a compensatory mechanism may protect dopamine neurons from neuronal death. These parkin mutant mice provide a valuable tool to better understand the preclin. deficits observed in patients with PD and to characterize the mechanisms leading to the degeneration of dopamine neurons that could provide new strategies for neuroprotection.
REFERENCE COUNT: 91 THERE ARE 91 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 8 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 2003:235026 HCAPLUS
DOCUMENT NUMBER: 139:143701
TITLE: Synthesis of a biotin-tagged photoaffinity probe of 2-azetidinone **cholesterol** absorption **inhibitors**
AUTHOR(S): Frick, Wendelin; Bauer-Schafer, Andrea; Bauer, Jochen; Girbig, Frank; Corsiero, Daniel; **Heuer, Hubert**; Kramer, Werner
CORPORATE SOURCE: Disease Group Metabolic Diseases Industriepark Hochst, Aventis Pharma Deutschland GmbH, Frankfurt am Main, D-65926, Germany
SOURCE: Bioorganic & Medicinal Chemistry (2003), 11(8), 1639-1642
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal
LANGUAGE: English
AB The design and synthesis of a biotin-tagged photoreactive analog C-4 of the **cholesterol** absorption **inhibitor** Ezetimibe is described. Photoaffinity labeling of **intestinal** brush border membrane vesicles with C-4 and subsequent streptavidin-biotin chromatog. leads to selective extraction of a 145 kDa integral membrane protein as the mol. target for **cholesterol** absorption **inhibitors**.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 9 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 2003:903740 HCAPLUS
DOCUMENT NUMBER: 140:179480
TITLE: Time sequence of maturation of dystrophic neurites associated with Aβ deposits in APP/PS1 transgenic mice
AUTHOR(S): Blanchard, Veronique; Moussaoui, Saliha; Czech, Christian; Touchet, Nathalie; Bonici, Bruno; Planche, Michel; **Canton, Thierry**; Jedidi, Iness; Gohin, Micheline; Wirths, Oliver; Bayer, Thomas A.; Langui, Dominique; Duyckaerts, Charles; Tremp, Gunter; **Pradier, Laurent**
CORPORATE SOURCE: Neurodegenerative Disease Group, Centre de Recherche de Paris, Vitry sur Seine, 94403, Fr.
SOURCE: Experimental Neurology (2003), 184(1), 247-263
CODEN: EXNEAC; ISSN: 0014-4886
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several novel transgenic mouse models expressing different mutant APPs in combination with mutant PS1 have been developed. These models have been analyzed to investigate the formation and progressive alterations of dystrophic neurites (DNs) in relation to Aβ deposits. In the most aggressive model, Aβ deposits appear as early as 2.5 mo of age. Maturation of DNs was qual. quite similar among models and in some respect reminiscent of human AD pathol. From the onset of deposition, most if not all Aβ deposits were decorated with a high number of APP-, ubiquitin-, and MnSOD-immunoreactive DNs. Phosphorylated Tau DNs, however, appeared at a much slower rate and were more restricted. Mitochondrial dysfunction markers were observed in DNs: the frequency and the d. per deposit of DNs accumulating cytochrome c, cytochrome oxidase 1, and Bax progressively increased with age. Later, the burden of reactive DNs was reduced around large compact/mature deposits. In addition, the previously described phenomenon of early intraneuronal Aβ accumulation in our models was associated with altered expression of APP protein as well as oxidative and mitochondrial stress markers occasionally in individual neurons. The present study demonstrates that oxidative and mitochondrial stress factors are present at several phases of Aβ pathol. progression, confirming the neuronal dysfunction in APP transgenic mice.
REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 10 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 2003:327208 HCAPLUS
DOCUMENT NUMBER: 139:83282
TITLE: A risk for early-onset Alzheimer's disease associated with the APBB1 gene (FE65) intron 13 polymorphism
AUTHOR(S): Cousin, Emmanuelle; Hannequin, Didier; Ricard,

Sylvain; Mace, Sandrine; Genin, Emmanuelle; Chansac, Celine; Brice, Alexis; Dubois, Bruno; Frebourg, Thierry; Mercken, Luc; **Benavides, Jesus**; **Pradier, Laurent**; Campion, Dominique; Deleuze, Jean-Francois

CORPORATE SOURCE: Paris Research Center, Evry Genetics Center & Neurodegenerative Disease Group, Aventis Pharma, Vitry-sur-Seine, 94400, Fr.

SOURCE: Neuroscience Letters (2003), 342(1,2), 5-8
CODEN: NELED5; ISSN: 0304-3940

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Alzheimer's disease (AD) is a genetically complex neurodegenerative disorder and the leading cause of dementia of the elderly. Recently, Hu et al. suggested that a trinucleotide deletion in intron 13 of the APBB1 gene was a factor protecting against late-onset AD. We report here the results of a case/control study aimed at replicating this association Our study included 461 AD patients and 397 matched controls. We compared the allele and genotype frequencies of the polymorphism between the two groups but did not find any statistically significant difference (P=0.08 and P=0.09, resp.). By contrast, adjusting for age and sex, we found a slight risk associated with the deletion (odds ratio=1.47, 95% confidence interval=1.05-2.04). Stratification by age showed that the risk effect associated with the deletion concerned subjects aged less than 65 yr.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 11 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 11

ACCESSION NUMBER: 2002:471429 HCAPLUS

DOCUMENT NUMBER: 138:71094

TITLE: Amyloid precursor protein family-induced neuronal death is mediated by impairment of the neuroprotective calcium/calmodulin protein kinase IV-dependent signaling pathway

AUTHOR(S): Mbebi, Corinne; See, Violaine; Mercken, Luc; **Pradier, Laurent**; Muller, Ulrike; Loeffler, Jean-Philippe

CORPORATE SOURCE: Universite Louis Pasteur, Faculte de Medecine, EA 3433 Molecular signaling and neurodegeneration, Strasbourg, 67000, Fr.

SOURCE: Journal of Biological Chemistry (2002), 277(23), 20979-20990
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The aberrant metabolism of β-amyloid precursor protein (**APP**) and the progressive deposition of its derived fragment β-amyloid peptide are early and constant pathol. hallmarks of Alzheimer's disease. Because **APP** is able to function as a cell surface receptor, the authors investigated here whether a disruption of the normal function of **APP** may contribute to the pathogenic mechanisms in Alzheimer's disease. To this aim, the authors generated a specific chicken polyclonal antibody directed against the extracellular domain of **APP**, which is common with the β-amyloid precursor-like protein type 2. Exposure of cultured cortical neurons to this antibody (**APP**-Ab) induced cell death preceded by neurite degeneration, oxidative stress, and nuclear

condensation. Interestingly, caspase-3-like protease was not activated in this neurotoxic action suggesting a different mode of cell death than classical apoptosis. Further anal. of the mol. mechanisms revealed a calpain- and calcineurin-dependent proteolysis of the neuroprotective calcium/calmodulin-dependent protein kinase IV and its nuclear target protein cAMP responsive element binding protein. These effects were abolished by the G protein **inhibitor** pertussis toxin, strongly suggesting that **APP** binding operates via a GTPase-dependent pathway to cause neuronal death.

REFERENCE COUNT: 90 THERE ARE 90 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 12 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 12
ACCESSION NUMBER: 2002:81635 HCAPLUS
DOCUMENT NUMBER: 136:307775
TITLE: Increased Expression of Presenilin 2 **Inhibits** Protein Synthesis
AUTHOR(S): Gamliel, Amir; Teicher, Carmit; Michaelson, Daniel M.; **Pradier, Laurent**; Hartmann, Tobias; Beyreuther, Konrad; Stein, Reuven
CORPORATE SOURCE: Department of Neurobiochemistry, George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv-Jaffa, 69978, Israel
SOURCE: Molecular and Cellular Neuroscience (2002), 19(1), 111-124
CODEN: MOCNED; ISSN: 1044-7431
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mutations in the presenilin genes PS1 and PS2 are a major cause of early onset familial Alzheimer's disease (AD). Previous studies have suggested that presenilins have several functions, including γ-**secretase** activity. It was also shown that presenilin expression is increased in the brains of some AD patients and ischemic rodents. The present study examines the effect of increased presenilin expression on protein synthesis. We show here that overexpression of wild-type PS2 (PS2wt) or PS2 mutant containing the FAD mutation N141I (PS2mut) in various cell lines **inhibits** the synthesis of coexpressed reporter and endogenous proteins. Furthermore, endogenous PS2 seems to be needed for translation **inhibition** since PS2 null fibroblasts were translationally more active than PS2+/+ fibroblasts under conditions known to **inhibit** translation. Overexpression of PS1 also appeared to cause **inhibition** of protein synthesis, but its effect was much weaker than that of PS2. Taken together, the results suggest that increased expression of PS2 and possibly also of PS1 **inhibits** translation and that presenilins may function as regulators of protein synthesis. (c) 2002 Academic Press.

REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 13 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 13
ACCESSION NUMBER: 2001:24031 HCAPLUS
DOCUMENT NUMBER: 134:176079
TITLE: Identification of binding proteins for **cholesterol** absorption **inhibitors** as components of the **intestinal cholesterol** transporter
AUTHOR(S): Kramer, W.; Glombik, H.; Petry, S.; **Heuer, H.** ; Schafer, H.-L.; Wendler, W.; Corsiero, D.; Girbig,

F.; Weyland, C.
CORPORATE SOURCE: Disease Group Metabolic Diseases, Aventis Pharma Deutschland GmbH, Frankfurt am Main, D-65926, Germany
SOURCE: FEBS Letters (2000), 487(2), 293-297
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To identify protein components of the **intestinal cholesterol** transporter, rabbit small **intestinal** brush border membrane vesicles were submitted to photoaffinity labeling using photoreactive derivs. of 2-azetidinone **cholesterol** absorption **inhibitors**. An integral membrane protein of Mr 145.3±7.5 kDa was specifically labeled in brush border membrane vesicles from rabbit jejunum and ileum. Its labeling was concentration-dependently **inhibited** by the presence of **cholesterol** absorption **inhibitors** whereas bile acids, D-glucose, fatty acids or cephalexin had no effect. The **inhibitory** potency of 2-azetidinones to **inhibit** photolabeling of the 145 kDa protein correlated with their in vivo activity to **inhibit intestinal cholesterol** absorption. These results suggest that an integral membrane protein of Mr 145 kDa is (a component of) the **cholesterol** absorption system in the brush border membrane of small **intestinal** enterocytes.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 14 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 14
ACCESSION NUMBER: 1999:807208 HCAPLUS
DOCUMENT NUMBER: 132:146489
TITLE: Alterations of carbohydrate and lipid intermediary metabolism during **inhibition** of glucose-6-phosphatase in rats
AUTHOR(S): Herling, A. W.; Burger, H.-J.; Schubert, G.; Hemmerle, H.; **Schaefer, H.-L.**; Kramer, W.
CORPORATE SOURCE: H 821 Pharmacology, Hoechst Marion Roussel Deutschland GmbH, Frankfurt am Main, 65926, Germany
SOURCE: European Journal of Pharmacology (1999), 386(1), 75-82
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB S 4048 (1-[2-(4-Chloro-phenyl)-cyclopropylmethoxy]-3,4-dihydroxy-5-(3-imidazo[4,5-b]pyridin-1-yl-3-phenyl-acryloyloxy)-cyclohexanecarboxylic acid), a derivative of chlorogenic acid, specifically **inhibits** the glucose-6-phosphate translocating component T1 of the glucose-6-phosphatase system. Its pharmacol. effect was studied on carbohydrate and lipid parameters in rats. In starved and fed rats, S 4048 caused a dose-dependent reduction of blood glucose levels with a corresponding increase in hepatic and renal glycogen and glucose-6-phosphate. The major quant. route of carbon flux in the liver during S 4048-induced **inhibition** of the glucose-6-phosphatase activity seemed to be glycogenesis. Plasma free fatty acids were increased secondarily due to the S 4048-induced hypoglycemia. Hepatic triglycerides were increased possibly due to increased re-esterification of the readily available free fatty acids. Glucose-6-phosphate translocase **inhibitors** may be useful for exptl. studying aspects of type 1 glycogen storage disease in laboratory animals as well as for the therapeutic modulation of inappropriately high rates of hepatic glucose production in type 2 diabetes.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 15 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 15
ACCESSION NUMBER: 1999:178553 HCAPLUS
DOCUMENT NUMBER: 131:3766
TITLE: Mapping the **APP**/presenilin (PS) binding domains: the hydrophilic N-terminus of PS2 is sufficient for interaction with **APP** and can displace **APP**/PS1 interaction
AUTHOR(S): **Pradier, Laurent**; Carpentier, Nathalie; Delalonde, Laurence; Clavel, Nicole; Bock, Marie-Dominique; Buee, Luc; Mercken, Luc; Tocque, Bruno; Czech, Christian
CORPORATE SOURCE: Gene Medicine Department, Rhone-Poulenc Rorer, Vitry, 94400, Fr.
SOURCE: Neurobiology of Disease (1999), 6(1), 43-55
CODEN: NUDIEM; ISSN: 0969-9961
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mutations in presenilin 1 and presenilin 2 (PS1 and PS2, resp.) genes cause the large majority of familial forms of early-onset Alzheimer's disease. The phys. interaction between presenilins and **APP** has been recently described using coimmunopptn. With a similar technique, we confirmed this interaction and have mapped the interaction domains on both PS2 and **APP**. Using several carboxy-terminal truncated forms of PS2, we demonstrated that the hydrophilic amino terminus of PS2 (residues 1 to 87, PS2NT) was sufficient for interaction with **APP**. Interestingly, only a construct with a leader peptide for secretion (SecPS2NT) and not its cytosolic counterpart was shown to interact with **APP**. For **APP**, we could demonstrate interaction of PS2 with the last 100 but not the last 45 amino acids of **APP**, including therefore the Aβ region. Accordingly, SecPS2NT is capable of binding to Aβ-immunoreactive species in conditioned medium. In addition, a second region in the extracellular domain of **APP** also interacted with PS2. Comparable results with PS1 indicate that the two presenilins share similar determinants of binding to **APP**. Confirming these results, SecPS2NT is able to **inhibit** PS1/**APP** interaction. Such a competition makes it unlikely that the PS/**APP** interaction results from nonspecific aggregation of PS in transfected cells. The phys. interaction of presenilins with a region encompassing the Aβ sequence of **APP** could be causally related to the misprocessing of **APP** and the production of Aβ1-42. (c) 1999 Academic Press.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 16 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 16
ACCESSION NUMBER: 1996:612230 HCAPLUS
DOCUMENT NUMBER: 125:293960
TITLE: Molecular cloning, functional expression, pharmacological characterization and chromosomal localization of the human metabotropic glutamate receptor type 3
AUTHOR(S): Emile, Lydia; Mercken, Luc; Apiou, Francoise; **Pradier, Laurent**; Bock, Marie-Dominique; Menager, Jean; Clot, Josette; Doble, Adam; Blanchard, Jean-Charles

CORPORATE SOURCE: Rhone-Poulenc Rorer SA, Centre de Recherche de Vitry-Alfortville, Vitry sur Seine, 94400, Fr.
SOURCE: Neuropharmacology (1996), 35(5), 523-530
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Glutamic acid is the major excitatory amino acid of the central nervous system which interacts with two receptor families, the ionotropic and metabotropic glutamate receptors. The metabotropic glutamate receptors (mGluRs) are coupled to G proteins and can be divided into three subgroups based on their sequence homol., signal transduction pathway and pharmacol. In this study, we describe the cloning of the cDNA encoding the human metabotropic glutamate receptor type 3 (**HmGluR3**). It was obtained by reverse transcription-polymerase chain reaction (RT-PCR) with degenerate oligonucleotides corresponding to highly conserved sequences between rat mGluRs. The receptor shows 879 amino acids with 96% amino acid sequence identity with rat mGluR3. It is strongly expressed in fetal and adult whole brain, especially in caudate nucleus and corpus callosum. The gene was identified by fluorescence in situ hybridization on chromosome 7 band q22. Activation of the human mGluR3, permanently expressed in Baby Hamster Kidney (BHK) cells, by excitatory amino acids **inhibits** the forskolin-stimulated accumulation of intracellular cAMP. The rank order of potency is L-glutamic acid>> (1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid ((1S,3R)-ACPD)»ibotenic acid >quisqualic acid. (RS)-α-methyl-4-carboxyphenylglycine [(RS)-MCPG, 1 mM] is without effect on **inhibition** of forskolin-induced cAMP accumulation by L-glutamic acid.

L26 ANSWER 17 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 17
ACCESSION NUMBER: 1993:420435 HCAPLUS
DOCUMENT NUMBER: 119:20435
TITLE: Inhibition by riluzole of electrophysiological responses mediated by rat kainate and NMDA receptors expressed in Xenopus oocytes
AUTHOR(S): Debono, Marc Williams; Le Guern, Joelle; **Canton, Thierry**; Doble, Adam; **Pradier, Laurent**
CORPORATE SOURCE: Dep. Biol., Rhone-Poulenc Rorer S. A., Vitry sur Seine, 94403, Fr.
SOURCE: European Journal of Pharmacology (1993), 235(2-3), 283-9
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of riluzole, an anticonvulsant and neuroprotective compound, on excitatory amino acid-evoked currents were studied in Xenopus laevis oocytes injected with mRNA from rat whole brain or cortex. Responses to kainic acid were blocked by riluzole (IC50 = 167 μM) as well as by the quinoxalinedione antagonists 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX:IC50 = 0.21 μM) and 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo[f]quinoxaline (NBQX: IC50 = 0.043 μM). NMDA receptor antagonist 2-amino-phosphonovaleric acid 92-APV) yielded an IC50 of 6.1 μM in this system. The inhibition by both riluzole and 2-APV was reversible and did not appear to be use dependent, unlike that of the channel blocker MK-801 ([+]-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-1,10-imine maleate). It was impossible to demonstrate an interaction of riluzole with any of the known ligand sites on either the kainate or the radioligand binding studies. These results suggest a direct but non-competitive action of riluzole on ionotropic

glutamate receptors.

L26 ANSWER 18 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 18
ACCESSION NUMBER: 1990:456670 HCAPLUS
DOCUMENT NUMBER: 113:56670
TITLE: Tumor necrosis factor (TNF) and endotoxin prime effects of PAF in vivo
AUTHOR(S): **Heuer, H. O.**; Letts, G.; Meade, C. J.
CORPORATE SOURCE: Dep. Pharmacol., Boehringer Ingelheim, Ingelheim, D-6507, Germany
SOURCE: Journal of Lipid Mediators (1990), 2(Suppl.), S101-S108
CODEN: JLMEEG; ISSN: 0921-8319
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of the present study in NMRI mice was to investigate the action of platelet-activating factor (PAF) on mortality and **intestinal** transit velocity, the interaction of endotoxin or tumor necrosis factor (TNF) with the effect of PAF on these parameters and the effect of the PAF antagonist WEB 2086 on the endotoxin/TNF- and PAF-induced changes. PAF at a high dose (200 μg/kg i.v.) increased mortality and reduced transit velocity. This effect was **inhibited** by WEB 2086 (0.01-0.5 mg/kg i.p.) in a dose-dependent manner. Pretreatment with endotoxin (10 μg/kg i.v.) or TNF (40 μg/kg i.v.) enhanced the activity of PAF resulting in increased mortality and reduced transit velocity. This enhanced activity of PAF in the case of pretreatment with endotoxin or TNF occurred at doses at which PAF, endotoxin or TNF given alone did not affect these parameters. The ability of endotoxin or TNF to enhance the effect of PAF was maximal if the time delay between endotoxin and subsequent PAF administration was about 1-2 h. WEB 2086 (0.01-1 mg/kg i.p.) **inhibited** this priming in a dose-dependent fashion. These findings support suggestions of a role for PAF in endotoxin shock and TNF-associated shock-like syndrome.

L26 ANSWER 19 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 19
ACCESSION NUMBER: 1989:508737 HCAPLUS
DOCUMENT NUMBER: 111:108737
TITLE: Effects of a new and specific PAF-antagonist, WEB 2086, on PAF and endotoxin/tumor necrosis factor induced changes in mortality and **intestinal** transit velocity
AUTHOR(S): **Heuer, Hubert**
CORPORATE SOURCE: Dep. Pharmacol., Boehringer Ingelheim K.-G., Ingelheim, D-6507, Fed. Rep. Ger.
SOURCE: Progress in Clinical and Biological Research (1989), 308(Vienna Shock Forum, 2nd, 1988), 919-24
CODEN: PCBRD2; ISSN: 0361-7742
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Endotoxin at ≤40 μg/kg and platelet-activating factor (PAF) at ≤100 μg/kg did not alter the gastrointestinal transit time or prove lethal to young mice. Single doses of tumor necrosis factor (TNF) also had no effects at 0.5 or 1.0 mg/kg, i.v. Pretreatment with TNF or endotoxin increased the lethal effects of PAF. Pretreatment with WEB 2086 at 0.1-1.0 mg/kg, i.p., 15 min prior to PAF **inhibited** the **intestinal** transit velocity changes from PAF plus TNF or endotoxin. WEB 2086 at 0.01-1.0 mg/kg, i.p., given 15 min before, **inhibited** the lethal synergism between TNF and subsequent PAF.

L26 ANSWER 20 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 20
ACCESSION NUMBER: 1987:531594 HCAPLUS
DOCUMENT NUMBER: 107:131594
TITLE: Circadian rhythm in the membrane of circulating human blood cells: microviscosity and number of benzodiazepine binding sites. A search for regulation by plasma ions, nucleosides, proteins or hormones
AUTHOR(S): Levi, Francis; **Benavides, Jesus**; Touitou, Yvan; Quarteronet, Dominique; **Canton, Thierry** ; Uzan, Andre; Auzeby, Andre; Gueremy, Claude; Sulon, Jose; et al.
CORPORATE SOURCE: Fond. Adolphe de Rothschild, Paris, 75940, Fr.
SOURCE: Chronobiology International (1987), 4(2), 235-43
CODEN: CHBIE4; ISSN: 0742-0528
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Circadian rhythms in both the number of peripheral type binding sites for benzodiazepines in platelet membranes and the microviscosity of the erythrocyte membrane were demonstrated in healthy men. Neither variable appeared to be linked to each other, or be regulated by the plasma concns. of total or free cortisol, testosterone, K+, Mg2+, Ca2+, cAMP, cGMP, or proteins or by the erythrocyte concentration of Mg2+ or K+ or by the plasma cAMP:cGMP ratio or by the ratio of intra-erythrocyte:plasma concns. of Mg2+ or K+. A highly significant neg. correlation was found between the microviscosity of the erythrocyte membrane and the activity of the membrane-bound enzyme methyltransferase I. Such a correlation was validated both on raw data and on 24 h-means. A circadian rhythm in the activity of this enzyme was also demonstrated. Moreover, a highly significant correlation was also found between plasma transcortin concentration (TRC) and microviscosity, and between TRC and methyltransferase I activity. Such findings may constitute clues towards the understanding of the regulation of the circadian rhythm in the fluidity of the red blood cell membrane in man and guide future steps with regard to the role of this rhythm upon the availability of drug binding sites at the cell surface.

L26 ANSWER 21 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 21
ACCESSION NUMBER: 1986:546030 HCAPLUS
DOCUMENT NUMBER: 105:146030
TITLE: Circadian rhythm in peripheral type benzodiazepine binding sites in human platelets
AUTHOR(S): Levi, Francis; **Benavides, Jesus**; Touitou, Yvan; Quarterronet, Dominique; **Canton, Thierry** ; Uzan, Andre; Gueremy, Claude; Le Fur, Gerard; Reinberg, Alain
CORPORATE SOURCE: Fond. Adolphe de Rothschild, Paris, 75940, Fr.
SOURCE: Biochemical Pharmacology (1986), 35(15), 2623-5
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Peripheral benzodiazepine (I) receptors were found in platelet membranes from all human subjects examined and at all time points. Such sites demonstrated a high affinity (KD) for [3H]PK 11195 (a selective ligand for peripheral I binding sites) and a high capacity (Bmax). Nonetheless large interindividual differences in the 24-h mean values of Bmax, KD, and platelet count were observed A circadian rhythm was found and validated for both Bmax and platelet count, but not for KD. The maximum binding occurred at 0350 h; the difference between maximum values was .apprx.20% of the 24-h mean. Circadian changes in the binding capacity were not related to

either platelet count (differences in peak times of resp. circadian rhythms or the affinity (no circadian rhythm in KD). As a result, the circadian in the binding capacity most likely reflects that in the number of binding sites per platelet. Apparently, the expression of I binding sites in human platelet exhibits a circadian rhythm.

L26 ANSWER 22 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 22
ACCESSION NUMBER: 1986:123089 HCAPLUS
DOCUMENT NUMBER: 104:123089
TITLE: Biochemical characterization and quantitative autoradiographic study of the binding sites for indalpine, a 5-HT **reuptake inhibitor**, in cat brain
AUTHOR(S): **Benavides, J.**; Malgouris, C.; Daniel, M.; Savaki, H.; Uzan, A.; Gueremy, C.; Le Fur, G.
CORPORATE SOURCE: Coll. France, Paris, 75231/05, Fr.
SOURCE: Encephale (1985), 11(6), 247-54
CODEN: ENCEAN; ISSN: 0013-7006
DOCUMENT TYPE: Journal
LANGUAGE: French
AB Autoradiog. and biochem. (competitive displacement) studies with cat brain slices showed that 3H-labeled indalpine [63758-79-2] bound with high affinity to serotoninergic receptors, as shown previously for the rat brain. The total number of binding sites was 146 fmol/mg protein, and the affinity constant was 2.6 mM. These sites could be differentiated from [3H]imipramine binding sites by their requirement for Na+ and their competitive **inhibition** by serotonin. Color-coded images of the distribution of the binding sites in various areas of the cat brain are presented. This distribution suggested that indalpine would have a stronger effect on the limbic system than on the extrapyramidal system, which is consistent with its known antidepressant properties in humans.

L26 ANSWER 23 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:681037 HCAPLUS
DOCUMENT NUMBER: 145:145534
TITLE: Preparation of sulfonyl pyrrolidines, and their use for increasing blood high-density lipoprotein level for treating dyslipidemia, diabetes and related diseases
INVENTOR(S): Keil, Stefanie; **Schaefer, Hans-Ludwig**; Glien, Maike; Guessregen, Stefan; Wendler, Wolfgang; Esswein, Marion
PATENT ASSIGNEE(S): Sanofi-Aventis Deutschland GmbH, Germany
SOURCE: PCT Int. Appl., 169 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006072393	A2	20060713	WO 2005-EP13772	20051221

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC,

VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.: DE 2005-102005000666A 20050104
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention is related to substituted sulfonyl pyrrolidines, including compds. of formula I [R1 = fluoro/alkyl, (un)substituted Ph, heterocyclyl, etc.; R2 = alkyl, (un)substituted Ph, heterocyclyl, etc.; R3-R5 = independently H, F, Cl, Br, NO2, alkyl, Ph, etc.; with the exclusion of certain compds.], and their physiol. acceptable salts, and their use as drugs for increasing blood HDL level. E.g., a multi-step synthesis starting from 4-methylbenzaldehyde, was given for pyrrolidine trans-II•TFA. I increased ATP-binding cassette protein A1 (ABCA1) expression and thereby increased production of **cholesterol** in blood HDL. I are useful for treating dyslipidemia, coronary circulation diseases, arteriosclerosis, diabetes, and metabolic syndrome.

L26 ANSWER 24 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:857559 HCAPLUS
DOCUMENT NUMBER: 141:314568
TITLE: Novel diphenyl azetidinone with improved physiological characteristics, corresponding production method, medicaments containing said compound and use of the latter
INVENTOR(S): Jaehne, Gerhard; Frick, Wendelin; Lindenschmidt, Andreas; Flohr, Stefanie; **Heuer, Hubert**; **Schaefer, Hans-Ludwig**; Kramer, Werner; Galia, Eric; Glombik, Heiner
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

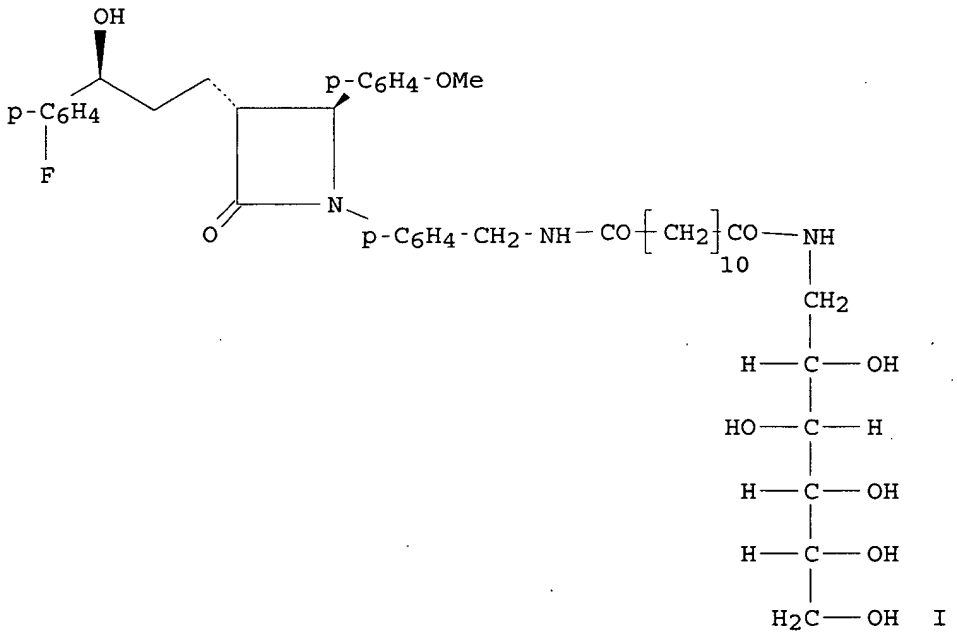
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004087655	A1	20041014	WO 2004-EP2690	20040316

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10314610	A1	20041104	DE 2003-10314610		20030401
AU 2004226287	A1	20041014	AU 2004-226287		20040316
CA 2520689	AA	20041014	CA 2004-2520689		20040316
EP 1613589	A1	20060111	EP 2004-720854		20040316
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK					
BR 2004008920	A	20060328	BR 2004-8920		20040316
CN 1768034	A	20060503	CN 2004-80008497		20040316
US 2005020563	A1	20050127	US 2004-813954		20040331
NO 2005005001	A	20051027	NO 2005-5001		20051027
PRIORITY APPLN. INFO.:			DE 2003-10314610	A	20030401
			US 2003-494456P	P	20030811
			WO 2004-EP2690	W	20040316

OTHER SOURCE(S): MARPAT 141:314568

GI



I

AB The invention relates to a novel di-Ph azetidinone (I) and its physiol. compatible salts, to a method for its production, to medicaments containing said compound and to the use of the latter. Said compound is suitable for use for example as a hypolipidemic agent. Thus, dodecanedioic acid was reacted with thionyl chloride followed by MeOH to give a monomethyl ester, which was then reacted with glucamine and deesterified to give the monoamide intermediate (II). II was reacted with the previously known (2S,3R)-1-(4-aminomethylphenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-methoxyphenyl)azetidin-2-one to give I in 32% yield. In in vitro tests on mice, I had ED50 0.005 mg/mouse for 50% reduction of liver 14C-labeled cholesterol. In solubility tests, compared to a similar reference compound, I had better solubility in water, at pH's 1.2, 4.5, 6.8, and 8.0, and in both fasted-

(28 μg/mL vs 5) and fed-state simulating intestinal fluids (454 μg/mL vs 18) (FaSSIF and FeSSIF).
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 25 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:1128525 HCAPLUS
DOCUMENT NUMBER: 142:69887
TITLE: Genetic diagnosis of Alzheimer's disease susceptibility by detection of gene ABCA2 polymorphism
INVENTOR(S): Mace, Sandrine; Ricard, Sylvain; Cousin, Emmanuelle; **Pradier, Laurent**; **Benavides, Jesus**; Deleuze, Jean Francois
PATENT ASSIGNEE(S): Aventis Pharma S.A., Fr.
SOURCE: Fr. Demande, 41 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2856409	A1	20041224	FR 2003-7501	20030620
AU 2004249919	A1	20041229	AU 2004-249919	20040617
CA 2529633	AA	20041229	CA 2004-2529633	20040617
WO 2004113568	A2	20041229	WO 2004-FR1509	20040617
WO 2004113568	A3	20050506		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005003417	A1	20050106	US 2004-869977	20040617
EP 1639139	A2	20060329	EP 2004-767370	20040617
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
CN 1809645	A	20060726	CN 2004-80017275	20040617
BR 2004011658	A	20060808	BR 2004-11658	20040617
NO 2006000257	A	20060118	NO 2006-257	20060118

PRIORITY APPLN. INFO.:			
	FR 2003-7501	A	20030620
	US 2003-496859P	P	20030821
	WO 2004-FR1509	W	20040617

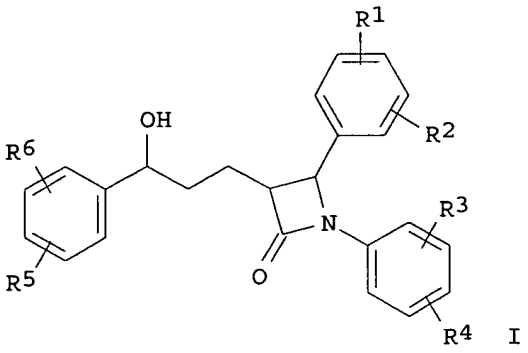
AB The invention relates to a method of diagnosis and prediction of Alzheimer's disease. The method is based on the detection of the presence or absence of the polymorphism in the minority allele rs908832 of gene ABCA2. The presence of the polymorphic allele rs908832 of gene ABCA2 indicates that the subject is in the stage of developing Alzheimer's disease or has an increased risk to develop the disease.
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 26 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:2851 HCAPLUS
DOCUMENT NUMBER: 140:59508
TITLE: Preparation of diphenylazetidinones substituted by acidic groups as hypolipidemics.
INVENTOR(S): Jaehne, Gerhard; Frick, Wendelin; Flohr, Stefanie; Lindenschmidt, Andreas; Glombik, Heiner; Kramer, Werner; **Heuer, Hubert**; **Schaefer, Hans-Ludwig**
PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004000805	A1	20031231	WO 2003-EP5816		20030604
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
DE 10227508	A1	20040108	DE 2002-10227508		20020619
CA 2490112	AA	20031231	CA 2003-2490112		20030604
AU 2003238210	A1	20040106	AU 2003-238210		20030604
EP 1517891	A1	20050330	EP 2003-735535		20030604
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003011896	A	20050405	BR 2003-11896		20030604
CN 1662495	A	20050831	CN 2003-814332		20030604
JP 2005533073	T2	20051104	JP 2004-514661		20030604
NZ 537302	A	20060630	NZ 2003-537302		20030604
US 2004067913	A1	20040408	US 2003-463388		20030618
ZA 2004009380	A	20051123	ZA 2004-9380		20041122
NO 2005000134	A	20050318	NO 2005-134		20050111
PRIORITY APPLN. INFO.:			DE 2002-10227508	A	20020619
			US 2002-418678P	P	20021015
			WO 2003-EP5816	W	20030604

OTHER SOURCE(S): MARPAT 140:59508
GI



I

AB Title compds. [I; R1-R6 = H, F, Cl, Br, iodo, CF3, NO2, N3, CN, CO2H, CO2alkyl, CONH2, CONHalkyl, C0-30-alkylene-(LAG)n, etc.; n = 1-5; ≥1 C of the alkylenes may be replaced by SO0-2, O, CO, CS, CH:CH, C.tplbond.C, alkylimino, phenylimino, alkylphenylimino, etc.; LAG = (CH2)1-10-SO3H, (CH2)0-10-P(O)(OH)2, (CH2)0-10-OP(O)(OH)2, (CH2)0-10CO2H; with provisos], were prepared Thus, 4-[5-(tert-butyldimethylsilyloxy)-5-(4-fluorphenyl)-1-(4-methoxyphenyl)-2-(2-oxo-4-phenyloxazolidin-3-carbonyl)pentylamino]benzonitrile (preparation given) in Me tert-Bu ether was treated with N,O-bis(trimethylsilyl)acetamide and Bu4NF in THF and the mixture was stirred 2 h at room temperature to give 4-[3-[3-(tert-butyldimethylsilyloxy)-3-(4-fluorophenyl)propyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]benzonitrile. This was converted to 4-[4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]benzylamino]butane-1-sulfonic acid in several steps. The latter **inhibited cholesterol** uptake by mouse liver with ED50 = 1.0 mg/mouse orally.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 27 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:2850 HCAPLUS
DOCUMENT NUMBER: 140:77013
TITLE: Preparation of diphenylazetidinones for the treatment of hyperlipidemia, arteriosclerosis and hypercholesterolemia
INVENTOR(S): Jaehne, Gerhard; Frick, Wendelin; Flohr, Stefanie; Lindenschmidt, Andreas; Glombik, Heiner; Kramer, Werner; **Heuer, Hubert; Schaefer, Hans-Ludwig**
PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004000804	A1	20031231	WO 2003-EP5815	20030604

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,

PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10227506	A1	20040108	DE 2002-10227506	20020619
CA 2490109	AA	20031231	CA 2003-2490109	20030604
AU 2003242616	A1	20040106	AU 2003-242616	20030604
EP 1517892	A1	20050330	EP 2003-760591	20030604
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003011940	A	20050405	BR 2003-11940	20030604
CN 1662493	A	20050831	CN 2003-814087	20030604
NZ 537304	A	20051028	NZ 2003-537304	20030604
JP 2005533072	T2	20051104	JP 2004-514660	20030604
US 2004082561	A1	20040429	US 2003-463807	20030618
NO 2005000073	A	20050106	NO 2005-73	20050106
PRIORITY APPLN. INFO.:			DE 2002-10227506 A	20020619
			US 2002-411984P P	20020919
			WO 2003-EP5815 W	20030604

OTHER SOURCE(S): MARPAT 140:77013
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R1, R2, R3, R4, R5, R6 = (un)substituted alkylene-(LAG)n; n = 1-5; LAG = sugar; amino sugar; amino acid, etc.] and their pharmaceutically acceptable salts were prepared For example, N-alkylation of 1,4-diazabicyclo[2.2.2]octane with benzyl bromide II, e.g., prepared from 1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone and 1,2-bisbromomethylbenzene, afforded diphenylazetidinone III. In rat liver chloresterol absorption assays, 26-examples of compds. I exhibited EC50 values ranging from 0.03-<1.0 (mg/mouse), e.g., the EC50 value of diphenylazetidinone III was 0.3. Compds. I are claimed useful for the treatment of hyperlipidemia, arteriosclerosis and hypercholesterolemia.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 28 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:2849 HCAPLUS
DOCUMENT NUMBER: 140:77012
TITLE: Preparation of diphenylazetidinones for the treatment of hyperlipidemia, arteriosclerosis, and hypercholesterolemia
INVENTOR(S): Jaehne, Gerhard; Frick, Wendelin; Flohr, Stefanie; Lindenschmidt, Andreas; Glombik, Heiner; Kramer, Werner; **Heuer, Hubert**; **Schaefer, Hans-ludwig**
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004000803	A1	20031231	WO 2003-EP5814	20030604
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10227507	A1	20040108	DE 2002-10227507	20020619
CA 2490108	AA	20031231	CA 2003-2490108	20030604
AU 2003238209	A1	20040106	AU 2003-238209	20030604
EP 1517890	A1	20050330	EP 2003-735534	20030604
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003011984	A	20050426	BR 2003-11984	20030604
CN 1662494	A	20050831	CN 2003-814093	20030604
JP 2005533071	T2	20051104	JP 2004-514659	20030604
NZ 537303	A	20060630	NZ 2003-537303	20030604
US 2004077623	A1	20040422	US 2003-463789	20030618
NO 2005000088	A	20050106	NO 2005-88	20050106
PRIORITY APPLN. INFO.:			DE 2002-10227507 A	20020619
			US 2002-411981P P	20020919
			WO 2003-EP5814 W	20030604

OTHER SOURCE(S): MARPAT 140:77012
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R1, R2, R3, R4, R5, R6 = (un)substituted alkylene-(LAG)n; n = 1-5; LAG = sugar; amino sugar; amino acid, etc.] and their pharmaceutically acceptable salts were prepared For example, condensation of benzonitrile II e.g., prepared from 3-[5-(4-fluorophenyl)-5-hydroxypentanoyl]-4-phenyloxazolidin-2-one in 4-steps, and hydroxylamine hydrochloride afforded N-hydroxybenzenecarboximidamide III. In rat liver **cholesterol** absorption assays, 14-examples of compds. I exhibited EC50 values ranging from 0.03-<1.0 (mg/mouse), e.g., the EC50 value of N-hydroxybenzenecarboximidamide III was 0.1. Compds. I are claimed useful for the treatment of hyperlipidemia, arteriosclerosis, and hypercholesterolemia.

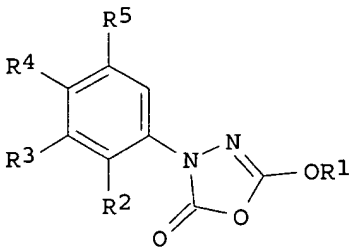
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 29 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:696877 HCAPLUS
DOCUMENT NUMBER: 139:214472
TITLE: Preparation of 5-alkoxy-3-phenyl-1,3,4-oxadiazol-2(3H)-ones as **inhibitors** of pancreatic lipase
INVENTOR(S): Schoenafinger, Karl; Petry, Stefan; Mueller, Guenter; Bauer, Armin; **Heuer, Hubert Otto**

PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003072555	A1	20030904	WO 2003-EP1484		20030214
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
DE 10208987	A1	20030911	DE 2002-10208987		20020228
CA 2477031	AA	20030904	CA 2003-2477031		20030214
AU 2003226977	A1	20030909	AU 2003-226977		20030214
EP 1480960	A1	20041201	EP 2003-742936		20030214
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003007921	A	20041221	BR 2003-7921		20030214
JP 2005519085	T2	20050630	JP 2003-571261		20030214
CN 1639137	A	20050713	CN 2003-804783		20030214
US 2003181433	A1	20030925	US 2003-375247		20030227
US 6900233	B2	20050531			
NO 2004004090	A	20041104	NO 2004-4090		20040927
PRIORITY APPLN. INFO.:			DE 2002-10208987	A	20020228
			US 2002-365706P	P	20020319
			WO 2003-EP1484	W	20030214

OTHER SOURCE(S): MARPAT 139:214472
GI



I

AB Title compds. [I; R1 = C7-22 alkyl, (substituted by C4-20 alkoxy, C6-10 aryl, C6-10 aryloxy, or C4-12-alkoxy-C2-4-alkoxy) C2-4 alkyl; C7-C20 alkenyl, 3β- **cholestan**-3-yl; (substituted) Ph; R2-R5 = H, halo, NO2, (substituted) C1-4 alkyl, C1-9 alkyloxy, CF3, trifluoromethoxy, C6-10-aryl-C1-4-alkyloxy, C6-10 aryloxy, C6-10 aryl, C3-8 cycloalkyl, O-C3-8-cycloalkyl], were prepared for treating obesity. Thus, a mixture of 0.84 g [4-(trifluoromethoxy)phenyl]hydrazine, NMP, and pyridine was

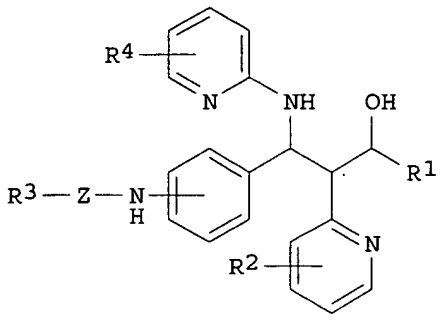
dropwise treated with 0.43 mL dodecyl chloroformate under ice cooling followed by slow heating at room temperature and stirring for 2 h to give 0.85 g 5-dodecyloxy-3-(4-trifluoromethoxyphenyl)-1,3,4-oxadiazol-2(3H)-one. The latter **inhibited** pancreatic lipase (PL) with IC50 = 0.03 μM.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 30 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:173467 HCAPLUS
DOCUMENT NUMBER: 138:215327
TITLE: Combined preparations, containing aryl-substituted propanolamine derivatives and other active substances for the treatment of hyperlipidemia
INVENTOR(S): Glombik, Heiner; Frick, Wendelin; **Schaefer, Hans-Ludwig**; Kramer, Werner
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003018059	A2	20030306	WO 2002-EP8907		20020809
WO 2003018059	A3	20031113			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
DE 10140170	A1	20030306	DE 2001-10140170		20010822
DE 10142455	A1	20030320	DE 2001-10142455		20010831
CA 2457974	AA	20030306	CA 2002-2457974		20020809
EP 1420826	A2	20040526	EP 2002-796212		20020809
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK					
BR 2002011995	A	20040928	BR 2002-11995		20020809
JP 2005505538	T2	20050224	JP 2003-522574		20020809
CN 1638801	A	20050713	CN 2002-816353		20020809
NZ 531292	A	20050826	NZ 2002-531292		20020809
NO 2004000726	A	20040219	NO 2004-726		20040219
PRIORITY APPLN. INFO.:			DE 2001-10140170	A	20010822
			DE 2001-10142455	A	20010831
			WO 2002-EP8907	W	20020809

OTHER SOURCE(S): MARPAT 138:215327
GI



I

AB The invention relates to mixts. of substances, containing propanolamine derivs. of formula (I), in which the functional groups have the indicated meanings, their physiol. acceptable salts and physiol. functional derivs. as well as other active substances for the treatment of metabolic disorders especially hyperlipidemia. The combination can also include antidiabetics, antiarthrytics etc. A typical capsule contains 100 mg of the drugs and 400 mg triglyceride mixture form coco fatty acids; other formulations are emulsions, tablets, dragees, and solns. Hamster that were fed with **cholesterol**-rich feed received orally the drug combination once daily for 10 days. Feces was analyzed for bile acids, blood lipid levels were measured and **cholesterol** was determined from liver.

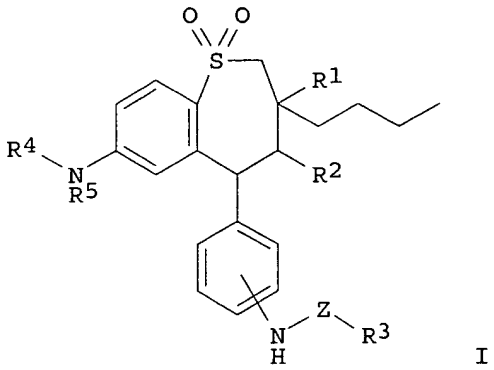
L26 ANSWER 31 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:173440 HCAPLUS
DOCUMENT NUMBER: 138:215326
TITLE: Combined preparations, containing 1,4-benzothiepine-1,1-dioxide derivatives and other active substances for the treatment of hyperlipidemia
INVENTOR(S): Glombik, Heiner; Frick, Wendelin; **Schaefer, Hans-Ludwig**; Kramer, Werner
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003018024	A1	20030306	WO 2002-EP8908	20020809
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10140169	A1	20030306	DE 2001-10140169	20010822
DE 10142456	A1	20030320	DE 2001-10142456	20010831
CA 2457976	AA	20030306	CA 2002-2457976	20020809

EP 1425018	A1	20040609	EP 2002-796213		20020809
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK					
BR 2002012031	A	20040803	BR 2002-12031		20020809
JP 2005501861	T2	20050120	JP 2003-522542		20020809
NZ 531293	A	20050826	NZ 2002-531293		20020809
NO 2004000702	A	20040519	NO 2004-702		20040218
PRIORITY APPLN. INFO.:			DE 2001-10140169	A	20010822
			DE 2001-10142456	A	20010831
			WO 2002-EP8908	W	20020809

OTHER SOURCE(S): MARPAT 138:215326

GI



I

AB The invention relates to mixts. of substances, containing 1,4-benzothiepine-1,1-dioxide derivs. of formula (I), in which the functional groups have the indicated meanings, their physiol. acceptable salts and physiol. functional derivs. as well as other active substances for the treatment of metabolic disorders especially hyperlipidemia. The combinations can also include antidiabetics, antiarthrytics etc. A typical capsule contains 100 mg of the drugs and 400 mg triglyceride mixture from coco fatty acids; other formulations are emulsions, tablets, dragees, and solns. Hamster that were fed with **cholesterol**-rich feed received orally the drug combination once daily for 10 days. Feces was analyzed for bile acids, blood lipid levels were measured and **cholesterol** was determined from liver.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 32 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:170325 HCAPLUS

DOCUMENT NUMBER: 138:215325

TITLE: Combined preparations, containing aryl-substituted propanol amine derivatives and other active substances for the treatment of hyperlipidemia

INVENTOR(S): Glombik, Heiner; Frick, Wendelin; **Schaefer, Hans-Ludwig**; Kramer, Werner

PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany

SOURCE: Ger. Offen., 10 pp.
CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

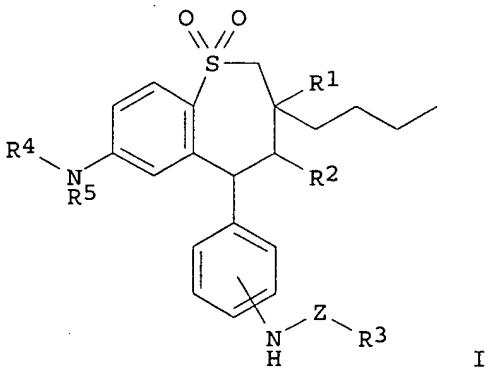
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10140170	A1	20030306	DE 2001-10140170	20010822
CA 2457974	AA	20030306	CA 2002-2457974	20020809
WO 2003018059	A2	20030306	WO 2002-EP8907	20020809
WO 2003018059	A3	20031113		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1420826	A2	20040526	EP 2002-796212	20020809
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002011995	A	20040928	BR 2002-11995	20020809
JP 2005505538	T2	20050224	JP 2003-522574	20020809
CN 1638801	A	20050713	CN 2002-816353	20020809
NZ 531292	A	20050826	NZ 2002-531292	20020809
US 2003158094	A1	20030821	US 2002-225802	20020822
ZA 2004000437	A	20050401	ZA 2004-437	20040121
NO 2004000726	A	20040219	NO 2004-726	20040219
PRIORITY APPLN. INFO.:			DE 2001-10140170 A	20010822
			DE 2001-10142455 A	20010831
			WO 2002-EP8907 W	20020809

OTHER SOURCE(S): MARPAT 138:215325

GI



I

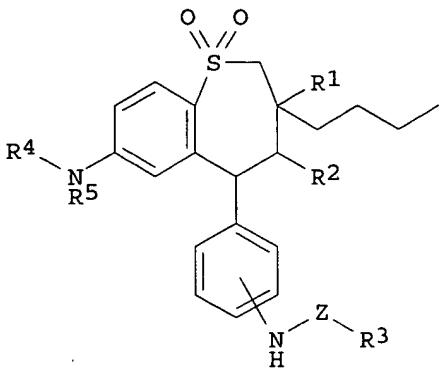
AB The invention relates to mixts. of substances, containing propanolamine derivs. of formula (I), in which the functional groups have the indicated meanings, their physiol. acceptable salts and physiol. functional derivs. as well as other active substances for the treatment of metabolic disorders especially hyperlipidemia. The combination can also include antidiabetics, antiarthrytics etc. A typical capsule contains 100 mg of

the drugs and 400 mg triglyceride mixture form coco fatty acids; other formulations are emulsions, tablets, dragees, and solns. The **inhibition** of sodium-dependent uptake of [3H]-taurocholate (TC) into brush border membrane vesicles was measured.

L26 ANSWER 33 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:170324 HCAPLUS
DOCUMENT NUMBER: 138:215324
TITLE: Combined preparations, containing 1,4-benzothiepine-1,1-dioxide derivatives and other active substances for the treatment of hyperlipidemia
INVENTOR(S): Glombik, Heiner; Frick, Wendelin; **Schaefer, Hans-Ludwig**; Kramer, Werner
PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE: Ger. Offen., 10 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
DE 10140169	A1	20030306	DE 2001-10140169		20010822
CA 2457976	AA	20030306	CA 2002-2457976		20020809
WO 2003018024	A1	20030306	WO 2002-EP8908		20020809
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
EP 1425018	A1	20040609	EP 2002-796213		20020809
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK					
BR 2002012031	A	20040803	BR 2002-12031		20020809
JP 2005501861	T2	20050120	JP 2003-522542		20020809
CN 1655792	A	20050817	CN 2002-816310		20020809
NZ 531293	A	20050826	NZ 2002-531293		20020809
US 2003158119	A1	20030821	US 2002-225841		20020822
US 2004097424	A1	20040520	US 2003-699967		20031103
ZA 2004000559	A	20041101	ZA 2004-559		20040126
NO 2004000702	A	20040519	NO 2004-702		20040218
PRIORITY APPLN. INFO.:			DE 2001-10140169	A	20010822
			DE 2001-10142456	A	20010831
			WO 2002-EP8908	W	20020809
			US 2002-225841	B1	20020822

OTHER SOURCE(S): MARPAT 138:215324
GI



I

AB The invention relates to mixts. of substances, containing 1,4-benzothiepine-1,1-dioxide derivs. of formula (I), in which the functional groups have the indicated meanings, their physiol. acceptable salts and physiol. functional derivs. as well as other active substances for the treatment of metabolic disorders especially hyperlipidemia. The combination can also include antidiabetics, antiarthrytics etc. A typical capsule contains 100 mg of the drugs and 400 mg triglyceride mixture form coco fatty acids; other formulations are emulsions, tablets, dragees, and solns. The **inhibition** of sodium-dependent uptake of [3H]-taurocholate (TC) into brush border membrane vesicles was measured.

L26 ANSWER 34 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:496163 HCAPLUS
DOCUMENT NUMBER: 140:214414
TITLE: Characterization and identification of the **intestinal cholesterol** uptake system
AUTHOR(S): Kramer, W.; Girbig, F.; Corsiero, D.; Burger, K.; Fahrenholz, F.; Glombik, H.; **Heuer, H.**
CORPORATE SOURCE: Abt. D.G. Stoffwechsel, Aventis Pharma Deutschland, Frankfurt, D-65926, Germany
SOURCE: Falk Symposium (2003), 129(Bile Acids: From Genomics to Disease and Therapy), 147-160
CODEN: FASYDI; ISSN: 0161-5580
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review presents evidence that both **cholesterol** and **cholesterol** absorption **inhibitors** interact at the level of the brush-border membrane with small **intestinal** enterocytes. A 145 kDa membrane protein is the mol. target for **cholesterol** absorption **inhibitors** catalyzing the first step of **intestinal cholesterol** absorption, the movement of **cholesterol** from mixed micelles across the brush-border membrane into the enterocyte. During this step, **cholesterol** interacts not with the 145 kDa, but with an integral 80 kDa membrane protein. ABC G5 and G8 probably pump out free **cholesterol** across the brush-border membrane after **cholesterol** has entered the cell via catalysis by the 145 kDa protein.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 35 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:487559 HCAPLUS
DOCUMENT NUMBER: 137:63115
TITLE: Preparation of diphenylazetidinone derivatives as hypolipidemic agents
INVENTOR(S): Glombik, Heiner; Kramer, Werner; Flohr, Stefanie; Frick, Wendelin; **Heuer, Hubert**; Jaehne, Gerhard; Lindenschmidt, Andreas; **Schaefer, Hans-Ludwig**
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002050068	A1	20020627	WO 2001-EP14532	20011211
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10064402	A1	20020627	DE 2000-10064402	20001221
DE 10154520	A1	20031002	DE 2001-10154520	20011107
CA 2431985	AA	20020627	CA 2001-2431985	20011211
AU 2002019173	A5	20020701	AU 2002-19173	20011211
EE 200300237	A	20030815	EE 2003-237	20011211
EP 1345932	A1	20030924	EP 2001-271371	20011211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001016482	A	20040203	BR 2001-16482	20011211
JP 2004516293	T2	20040603	JP 2002-551564	20011211
NZ 526592	A	20041126	NZ 2001-526592	20011211
RU 2275370	C2	20060427	RU 2003-122219	20011211
US 2002128252	A1	20020912	US 2001-21028	20011219
US 6498156	B2	20021224		
ZA 2003004092	A	20040419	ZA 2003-4092	20030527
ZA 2003004095	A	20040419	ZA 2003-4095	20030527
NO 2003002733	A	20030814	NO 2003-2733	20030616
HK 1059936	A1	20060127	HK 2004-102849	20040422

PRIORITY APPLN. INFO.:
DE 2000-10064402 A 20001221
DE 2001-10154520 A 20011107
WO 2001-EP14532 W 20011211

OTHER SOURCE(S): MARPAT 137:63115
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The compds. are suited for use e.g. as hypolipidemic drugs. The invention discloses preparation of diphenylazetidinone derivs. such as I [R1, R2, R3, R4,

R5, R6 = C0-C30-alkylene-L {optionally containing O, CO, CH:CH, C.tplbond.C, N(alkyl), N(alkylphenyl), NH}, H, F, Cl, Br, I, CF3, NO2, CN, CO2H, CO2(alkyl), CONH2, CONH(alkyl), CON(alkyl)2, alkyl, alkenyl, alkynyl, O-alkyl, SO2NH2, SO2NH(alkyl) SO2N(alkyl)2, S-(alkyl), SO(alkyl), (un)substituted S(CH2)nPh, SO(CH2)nPh, SO2(alkyl), SO2(CH2)nPh, NH2, NH(alkyl), N(alkyl)2, NH(acyl), (un)substituted Ph, O(CH2)nPh; n = 0-6; L = II; R7, R9, R10 = Me, Et, Pr, butyl; R8 = H, OH, NH2, NH(alkyl)], and their physiol. acceptable salts, for their use as hypolipidemic agents. Thus, 1,2-diphenylazetidinone derivative III·trifluoroacetate (IV) was prepared via a multistep synthetic sequence starting from 7-[3-(3-butyl-7-dimethylamino-3-ethyl-4-hydroxy-1,1-dioxo-2,3,4,5-tetrahydro-1H-benzo[b]thiepin-5-yl)-phenylcarbamoyl]-heptanoic acid and 4-(4-aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxyphenyl]-azetidin-2-one. Azetidinone IV was tested for its cholesterol lowering ability [ED50 = 0.01 mg/mouse].

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 36 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:487551 HCAPLUS
DOCUMENT NUMBER: 137:63114
TITLE: Preparation of diphenylazetidinone derivatives and their use as hypolipidemic agents
INVENTOR(S): Glombik, Heiner; Kramer, Werner; Flohr, Stefanie; Frick, Wendelin; **Heuer, Hubert**; Jaehne, Gerhard; Lindenschmidt, Andreas; **Schaefer, Hans-Ludwig**
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002050060	A1	20020627	WO 2001-EP14533	20011211
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10064402	A1	20020627	DE 2000-10064402	20001221
CA 2431995	AA	20020627	CA 2001-2431995	20011211
AU 2002031688	A5	20020701	AU 2002-31688	20011211
EE 200300238	A	20030815	EE 2003-238	20011211
EP 1345924	A1	20030924	EP 2001-991821	20011211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001016322	A	20031014	BR 2001-16322	20011211
JP 2004516289	T2	20040603	JP 2002-551556	20011211
NZ 526594	A	20040827	NZ 2001-526594	20011211
RU 2282628	C2	20060827	RU 2003-122217	20011211
US 2002128253	A1	20020912	US 2001-21044	20011219

US 6703386	B2	20040309			
ZA 2003004092	A	20040419	ZA 2003-4092		20030527
ZA 2003004095	A	20040419	ZA 2003-4095		20030527
NO 2003002735	A	20030806	NO 2003-2735		20030616
HK 1060119	A1	20060203	HK 2004-102853		20040422
PRIORITY APPLN. INFO.:			DE 2000-10064402	A	20001221
			DE 2001-10154518	A	20011107
			WO 2001-EP14533	W	20011211

OTHER SOURCE(S): MARPAT 137:63114
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention discloses preparation of diphenylazetidinone derivs. such as I [R1, R2, R3, R4, R5, R6 = C0-C30-alkylene-L {optionally containing O, CO, CH:CH, C.tplbond.C, N(alkyl), N(alkylphenyl), NH}, H, F, Cl, Br, I, CF3, NO2, CN, CO2H, CO2(alkyl), CONH2, CONH(alkyl), CON(alkyl)2, alkyl, alkenyl, alkynyl, O-alkyl, SO2NH2, SO2NH(alkyl) SO2N(alkyl)2, S-(alkyl), SO(alkyl), (un)substituted S(CH2)nPh, SO(CH2)nPh, SO2(alkyl), SO2(CH2)nPh, NH2, NH(alkyl), N(alkyl)2, NH(acyl), (un)substituted Ph, O(CH2)nPh; n = 0-6; L = II; Rx, Ry, Rz = H, F, Cl, Br, I, CF3, NO2, CN, CO2H, CO2(alkyl), CONH2, O-alkyl], and their physiol. acceptable salts, for their use as hypolipidemic agents. Thus, 1,2-diphenylazetidinone derivative III·trifluoroacetate was prepared from 4-(3-aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]azetidinone via N-acylation with 11-{2-[3-hydroxy-3-phenyl-2-pyridin-2-yl-1-(pyridin-2-ylamino)propyl]-phenylcarbamoyl}-undecanoic acid. Azetidinone III was tested for its cholesterol lowering ability [ED50 = 0.003 mg/mouse].
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 37 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:487523 HCAPLUS
DOCUMENT NUMBER: 137:63113
TITLE: Method for producing novel 1,2-diphenylazetidinones, medicaments containing them, and their use for treating disorders of lipid metabolism
INVENTOR(S): Glombik, Heiner; Kramer, Werner; Flohr, Stefanie; Frick, Wendelin; **Heuer, Hubert**; Jaehne, Gerhard; Lindenschmidt, Andreas; **Schaefer, Hans-Ludwig**
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002050027	A1	20020627	WO 2001-EP14531	20011211
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,				

PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10064398	A1	20020627	DE 2000-10064398		20001221
DE 10152981	A1	20030508	DE 2001-10152981		20011026
CA 2431983	AA	20020627	CA 2001-2431983		20011211
AU 2002016097	A5	20020701	AU 2002-16097		20011211
EE 200300236	A	20030815	EE 2003-236		20011211
EP 1345895	A1	20030924	EP 2001-271353		20011211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
BR 2001016325	A	20031014	BR 2001-16325		20011211
JP 2004516280	T2	20040603	JP 2002-551524		20011211
NZ 526593	A	20050225	NZ 2001-526593		20011211
US 2002137689	A1	20020926	US 2001-21502		20011219
US 6992067	B2	20060131			
ZA 2003004093	A	20040423	ZA 2003-4093		20030527
NO 2003002734	A	20030818	NO 2003-2734		20030616
US 2005267038	A1	20051201	US 2005-155109		20050617
PRIORITY APPLN. INFO.:			DE 2000-10064398	A	20001221
			DE 2001-10152981	A	20011026
			WO 2001-EP14531	W	20011211
			US 2001-21502	A3	20011219

OTHER SOURCE(S): CASREACT 137:63113; MARPAT 137:63113
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to the compds. I [R1, R2, R3, R4, R5, R6 = C0-30-alkylene-LAG {optionally containing O, CO, CH:CH, C.tplbond.C, N(C1-6-alkyl), N(C1-6-alkylphenyl), NH}, H, F, Cl, Br, I, CF3, NO2, CN, CO2H, CO2(C1-6-alkyl), CONH, CONH(C1-6-alkyl), CON(C1-6-alkyl)2, C1-6-alkyl, C1-6-alkenyl, C1-6-alkynyl, O-(C1-6-alkyl), SO2NH2, SO2NH(C1-6-alkyl) SO2N(C1-6-alkyl)2, S-(C1-6-alkyl), SO(C1-6-alkyl), (un)substituted S(CH2)nPh, SO(CH2)nPh, SO2(C1-6-alkyl), SO2(CH2)nPh, NH2, NH(C1-6-alkyl), N(C1-6-alkyl)2, NH(C1-6-acyl), (un)substituted Ph, O(CH2)nPh; LAG = sugar residue, di-, tri-, tetrasaccharide, carbohydrate acid, amino sugar, amino acid, oligopeptide (2 - 9 residues), (trialkylammonium)alkyl, OSO3H] and to their physiol. acceptable salts, suitable, for example, as hypolipidemics. Thus, 1,2-diphenylazetidinone II [R10 = CO(CH2)11NHCO(CHOH)4CH2OH] was prepared from (methoxyphenyl)azetidinone II (R10 = H) via N-acylation with 12-[(2,3,4,5,6-pentahydroxyhexanoyl)amino]dodecanoic acid. Azetidinone II was tested for its cholesterol lowering ability [ED50 = 0.003 mg/mouse].
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 38 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:669829 HCAPLUS
DOCUMENT NUMBER: 135:356303
TITLE: The caspase-derived C-terminal fragment of β **APP** induces caspase-independent toxicity and triggers selective increase of Aβ42 in mammalian cells

AUTHOR(S): Dumanchin-Njock, Cecile; Alves da Costa, Cristine; Mercken, Luc; **Pradier, Laurent**; Checler, Frederic
CORPORATE SOURCE: Institut de Pharmacologie Moleculaire et Cellulaire, CNRS, Universite de Nice-Sophia Antipolis, Valbonne, 06560, Fr.
SOURCE: Journal of Neurochemistry (2001), 78(5), 1153-1161
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB During its physiopathol. maturation, the β-amyloid precursor protein undergoes several distinct proteolytic events by activities called **secretases**. In Alzheimer's disease, the main histol. hallmark called senile plaque is clearly linked to the overprodn. of the amyloid peptides Aβ40 and Aβ42, two highly aggregable β **APP** -derived fragments generated by combined cleavages by β- and γ- **secretases**. Recently, an alternative hydrolytic pathway was described, involving another category of proteolytic activities called caspases, responsible for the production of a 31 amino acids β **APP** C-terminal fragment called C31. C31 was reported to lower the viability of N2a cells but the exact mechanisms mediating C31-toxicity remained to be established. Here the authors show that the transient transfection of pSV2 vector encoding C31 lowers by about 80% TSM1 neuronal cells viability. Arguing against a C31-stimulated apoptotic response, the authors demonstrate by combined enzymic and immunol. approaches that C31 expression did not modulate basal or staurosporine-induced caspase 3-like activity and pro-caspase-3 activation. Furthermore, C31 did not modify Bax and p53 expressions, poly-(ADP-ribose)-polymerase cleavage and cytochrome c translocation into the cytosol. However, the authors established that C31 overexpression triggers selective increase of Aβ42 but not Aβ40 production by HEK293 cells expressing wild-type βAPP751. Altogether, the authors' data demonstrate that C31 induces a caspase-independent toxicity in TSM1 neurons and potentiates the pathogenic β **APP** maturation pathway by increasing selectively Aβ42 species in wild type-β **APP**-expressing human cells.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 39 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:795803 HCAPLUS
DOCUMENT NUMBER: 132:35625
TITLE: Amino acid containing benzo[b]thiepine 1,1-dioxide derivatives as hypolipemic agents
INVENTOR(S): Frick, Wendelin; Enhsen, Alfons; Glombik, Heiner; **Heuer, Hubert**
PATENT ASSIGNEE(S): Hoechst Marion Roussel Deutschland G.m.b.H., Germany
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964410	A1	19991216	WO 1999-EP3701	19990528
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,				

DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

DE 19825804	A1	19991216	DE 1998-19825804	19980610
DE 19825804	C2	20000824		
CA 2334775	AA	19991216	CA 1999-2334775	19990528
AU 9945019	A1	19991230	AU 1999-45019	19990528
AU 753275	B2	20021010		
EP 1086092	A1	20010328	EP 1999-927784	19990528
EP 1086092	B1	20021113		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
BR 9912188	A	20010410	BR 1999-12188	19990528
TR 200003634	T2	20010621	TR 2000-200003634	19990528
JP 2002517491	T2	20020618	JP 2000-553419	19990528
AT 227715	E	20021115	AT 1999-927784	19990528
ES 2182535	T3	20030301	ES 1999-927784	19990528
PT 1086092	T	20030331	PT 1999-927784	19990528
RU 2215001	C2	20031027	RU 2001-101491	19990528
CN 1127497	B	20031112	CN 1999-807171	19990528
TR 200003632	T2	20010420	TR 2000-200003632	19990529
PT 1086113	T	20040630	PT 1999-927802	19990529
ES 2215387	T3	20041001	ES 1999-927802	19990529
AU 761249	B2	20030529	AU 2000-53394	20000816
ZA 2000007060	A	20010718	ZA 2000-7060	20001130
ZA 2000007061	A	20010718	ZA 2000-7061	20001130
US 6387944	B1	20020514	US 2000-719047	20001207
US 2002045583	A1	20020418	US 2001-773772	20010202
US 6441022	B2	20020827		
HK 1036799	A1	20040402	HK 2001-107735	20011106
PRIORITY APPLN. INFO.:			DE 1998-19825804	A 19980610
			AU 1997-23266	A3 19970311
			WO 1999-EP3701	W 19990528
			US 1999-398315	A1 19990920

OTHER SOURCE(S): MARPAT 132:35625
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. such as I (mixture of diastereoisomers) were prepared as hypolipemic agents. Thus, I was prepared in 2 sequences from racemic II and Fmoc-D-lys(Boc)-OH, followed by removal of the Fmoc group with Et2NH. I was ≥20 times more active than 3 analogous comparison substances in tests of fecal separation of 14C-taurocholic acid in rats.
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 40 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:795802 HCAPLUS
DOCUMENT NUMBER: 132:22884
TITLE: Preparation of benzothiepine-1,1-dioxides as hypolipemics
INVENTOR(S): Frick, Wendelin; Enhsen, Alfons; Glombik, Heiner;

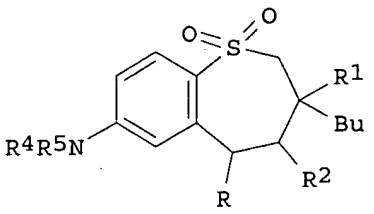
Heuer, Hubert
PATENT ASSIGNEE(S): Hoechst Marion Roussel Deutschland G.m.b.H., Germany
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964409	A2	19991216	WO 1999-EP3743	19990529
WO 9964409	A3	20000302		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19825804	A1	19991216	DE 1998-19825804	19980610
DE 19825804	C2	20000824		
TR 200003634	T2	20010621	TR 2000-200003634	19990528
ES 2182535	T3	20030301	ES 1999-927784	19990528
PT 1086092	T	20030331	PT 1999-927784	19990528
CN 1127497	B	20031112	CN 1999-807171	19990528
CA 2334773	AA	19991216	CA 1999-2334773	19990529
AU 9945031	A1	19991230	AU 1999-45031	19990529
AU 752633	B2	20020926		
EP 1086113	A2	20010328	EP 1999-927802	19990529
EP 1086113	B1	20040211		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
TR 200003632	T2	20010420	TR 2000-200003632	19990529
JP 2002517490	T2	20020618	JP 2000-553418	19990529
JP 3374129	B2	20030204		
NZ 508681	A	20020628	NZ 1999-508681	19990529
RU 2220141	C2	20031227	RU 2001-101499	19990529
AT 259372	E	20040215	AT 1999-927802	19990529
PT 1086113	T	20040630	PT 1999-927802	19990529
IL 140078	A1	20040831	IL 1999-140078	19990529
ES 2215387	T3	20041001	ES 1999-927802	19990529
BR 9911123	A	20060103	BR 1999-11123	19990529
US 6221897	B1	20010424	US 1999-398315	19990920
AU 761249	B2	20030529	AU 2000-53394	20000816
ZA 2000007060	A	20010718	ZA 2000-7060	20001130
ZA 2000007061	A	20010718	ZA 2000-7061	20001130
NO 2000006251	A	20010207	NO 2000-6251	20001208
US 2002045583	A1	20020418	US 2001-773772	20010202
US 6441022	B2	20020827		
HK 1039490	A1	20041210	HK 2001-107746	20011106
US 2003017996	A1	20030123	US 2002-201050	20020724
US 6642269	B2	20031104		
US 2004087648	A1	20040506	US 2003-606771	20030627
US 7019023	B2	20060328		

PRIORITY APPLN. INFO.:			
	DE 1998-19825804	A	19980610
	US 1996-13119P	P	19960311
	AU 1997-23266	A3	19970311
	WO 1999-EP3743	W	19990529

	US 1999-398315	A1 19990920
	US 2001-773772	A1 20010202
	US 2002-201050	A1 20020724

OTHER SOURCE(S): MARPAT 132:22884
GI



I

AB Title compds. [I; R = C6H4NHZR3; R1,R4,R5 = Me, Et, Pr, Bu; R2 = H, OH, amino(alkyl); R3 = sugar residue; Z = bond, carbonyl(alkylene), CONH, etc.] were prepared Thus, I [R = C6H4(NHR')-3, R1 = Et, R2 = OH, R4 = R5 = Me](II; R' = H) was amidated by penta-O-acetyl-D-gluconic acid and the product deprotected to give II (R' = gluconoyl) as a mixture of diastereomers. Data for biol. activity of I were given.

L26 ANSWER 41 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:602051 HCAPLUS
DOCUMENT NUMBER: 131:347939
TITLE: Substrate specificity of the ileal and the hepatic Na+/bile acid cotransporters of the rabbit. I. Transport studies with membrane vesicles and cell lines expressing the cloned transporters
AUTHOR(S): Kramer, Werner; Stengelin, Siegfried; Baringhaus, Karl-Heinz; Enhsen, Alfons; **Heuer, Hubert**; Becker, Wolfgang; Corsiero, Daniel; Girbig, Frank; Noll, Rudiger; Weyland, Claudia
CORPORATE SOURCE: DG Metabolic Diseases, Hoechst Marion Roussel Deutschland GmbH, Frankfurt am Main, D-65926, Germany
SOURCE: Journal of Lipid Research (1999), 40(9), 1604-1617
CODEN: JLPRAW; ISSN: 0022-2275
PUBLISHER: Lipid Research, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The substrate specificity of the ileal and the hepatic Na+/bile acid cotransporters was determined using brush border membrane vesicles and CHO cell lines permanently expressing the Na+/bile acid cotransporters from rabbit ileum or rabbit liver. The hepatic transporter showed a remarkably broad specificity for interaction with cholephilic compds. in contrast to the ileal system. The anion transport **inhibitor** diisothiocyanostilbene disulfonate (DIDS) is a strong **inhibitor** of the hepatic Na+/bile acid cotransporter, but does not show any affinity to its ileal counterpart. **Inhibition** studies and uptake measurements with about 40 different bile acid analogs differing in the number, position, and stereochem. of the hydroxyl groups at the steroid nucleus resulted in clear structure-activity relationships for the ileal and hepatic bile acid transporters. The affinity to the ileal and hepatic Na+/bile acid cotransport systems and the uptake rates by cell lines expressing those transporters as well as rabbit ileal brush border membrane vesicles is primarily determined by the substituents on the steroid

nucleus. Two hydroxy groups at position 3, 7, or 12 are optimal whereas the presence of three hydroxy groups decreased affinity. Vicinal hydroxy groups at positions 6 and 7 or a shift of the 7-hydroxy group to the 6-position significantly decreased the affinity to the ileal transporter in contrast to the hepatic system. 6-Hydroxylated bile acid derivs. are preferred substrates of the hepatic Na+/bile acid cotransporter. Surprisingly, the 3α-hydroxy group being present in all natural bile acids is not essential for high affinity interaction with the ileal and the hepatic bile acid transporter. The 3α-hydroxy group seems to be necessary for optimal transport of a bile acid across the hepatocyte canalicular membrane. A modification of bile acids at the 3-position therefore conserves the bile acid character thus determining the 3-position of bile acids as the ideal position for drug targeting strategies using bile acid transport pathways.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 42 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:812258 HCAPLUS
DOCUMENT NUMBER: 128:57465
TITLE: Use of **inhibitors** of cellular Na+/H+-exchangers for preparing a medicine for normalizing serum lipids
INVENTOR(S): Lang, Hans Jochen; Schwark, Jan Robert; Kleemann, Heinz Werner; Jung, Oliver; **Schaefer, Hans Ludwig**; Linz, Wolfgang; Kramer, Werner; Schoelkens, Bernward; Jansen, Hans Willi; Falk, Eugen
PATENT ASSIGNEE(S): Hoechst A.-G., Germany
SOURCE: Ger. Offen., 6 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19622222	A1	19971204	DE 1996-19622222	19960603
CA 2257299	AA	19971211	CA 1997-2257299	19970520
WO 9746226	A2	19971211	WO 1997-EP2548	19970520
WO 9746226	A3	19980305		
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9729576	A1	19980105	AU 1997-29576	19970520
AU 722166	B2	20000720		
EP 918515	A2	19990602	EP 1997-923937	19970520
EP 918515	B1	20050427		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
CN 1221339	A	19990630	CN 1997-195194	19970520
BR 9709516	A	19990810	BR 1997-9516	19970520
JP 2000506906	T2	20000606	JP 1998-500144	19970520
NZ 333095	A	20000825	NZ 1997-333095	19970520
RU 2211032	C2	20030827	RU 1999-100084	19970520
AT 293965	E	20050515	AT 1997-923937	19970520

PT 918515	T	20050630	PT 1997-923937	19970520
ES 2241049	T3	20051016	ES 1997-923937	19970520
PL 189950	B1	20051031	PL 1997-330412	19970520
ZA 9704828	A	19971203	ZA 1997-4828	19970602
NO 9805480	A	19990128	NO 1998-5480	19981124
KR 2000016240	A	20000325	KR 1998-709811	19981202
US 2004122096	A1	20040624	US 2003-680275	20031008
PRIORITY APPLN. INFO.:			DE 1996-19622222	A 19960603
			DE 1997-19712636	A 19970326
			WO 1997-EP2548	W 19970520
			US 1998-194749	B1 19981203
			US 2000-689692	B1 20001013

AB Na+/H+ exchangers (especially guanidine derivs.) are useful in medications for lowering serum lipid levels, treatment of hypercholesterolemia-related circulatory disorders, and prevention and treatment of atherosclerosis, endothelial dysfunction syndrome, cardiac hypertrophy, cardiomyopathy, coronary vasospasm, and myocardial infarct and of disorders secondary to these diseases. Thus, in rabbits receiving a **cholesterol**-rich diet, addition of 0.1% HOE 642 [(4-isopropyl-3-methanesulfonyl)benzoylguanidine methanesulfonate] to the diet decreased the serum **cholesterol**, VLDL, LDL, and HDL levels from 17.85, 5.68, 9.31, and 2.86 (control) to 7.95, 4.6, 2.1, and 1.8 mM, resp.

L26 ANSWER 43 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:161940 HCAPLUS
TITLE: Synthesis and SAR of trimeric bile acid reabsorption **inhibitors**: A new approach to lower **cholesterol**
AUTHOR(S): Glombik, H.; Baringhaus, K. -H.; Boeger, G.; Enhsen, A.; Falk, E.; Friedrich, M.; Hoffmann, A.; Kramer, W.; **Schaefer, H. L.**; et al.
CORPORATE SOURCE: HMR TA Metabolism Research, Frankfurt/Main, D-65926, Germany
SOURCE: Book of Abstracts, 213th ACS National Meeting, San Francisco, April 13-17 (1997), MEDI-108. American Chemical Society: Washington, D. C.
CODEN: 64AOAA
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

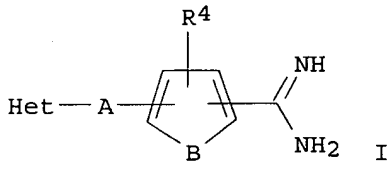
AB Recent attempts in antiatherosclerotic therapy focus on **cholesterol** lowering agents with new modes of action. With regard to resins and statins real progress is expected from non absorbable bile acid reabsorption **inhibitors** (BARI) that block the ileal transporter specific for bile acids. This will lead to increased excretion of bile acids, resynthesis from **cholesterol** in the liver and thus lowering of blood **cholesterol** by an indirect and non systemic mechanism. While there is some information available on the size and function of the ileal bile acid transporter, a detailed structure anal. of this transmembrane protein has not been performed. BARI with minimal absorption are designed and synthesized by combining bile acid moieties as recognition units via linkers to trivalent core structures such as Kemp's triacid. Linker chemical had to be developed for this purpose. A directing effect of the core unit is most important for activity at the primary target as tested in cell and animal models.

L26 ANSWER 44 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:308716 HCAPLUS
DOCUMENT NUMBER: 122:81416
TITLE: Heterocycle-containing amidine derivatives, their

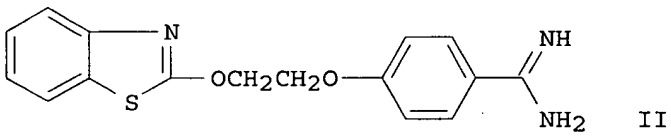
preparation, and use as LTB4 antagonists
INVENTOR(S): Renth, Ernst Otto; Schromm, Kurt; Anderskewitz, Ralf; Birke, Franz; Fuegner, Armin; **Heuer, Hubert**
PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Germany
SOURCE: Ger. Offen., 31 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4309285	A1	19940929	DE 1993-4309285	19930323
CA 2158994	AA	19940929	CA 1994-2158994	19940318
WO 9421616	A1	19940929	WO 1994-EP856	19940318
W: AT, AU, BG, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KR, KZ, LU, LV, NL, NO, NZ, PL, PT, RO, RU, SE, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9463780	A1	19941011	AU 1994-63780	19940318
EP 690849	A1	19960110	EP 1994-911191	19940318
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1124486	A	19960612	CN 1994-192207	19940318
JP 08508467	T2	19960910	JP 1994-520657	19940318
HU 73968	A2	19961028	HU 1995-2778	19940318
ZA 9401993	A	19940923	ZA 1994-1993	19940322
FI 9504491	A	19950922	FI 1995-4491	19950922
NO 9503763	A	19950925	NO 1995-3763	19950922
LV 11465	B	19961220	LV 1995-291	19950922
PRIORITY APPLN. INFO.:			DE 1993-4309285 A	19930323
			WO 1994-EP856 W	19940318

OTHER SOURCE(S): MARPAT 122:81416
GI



I



II

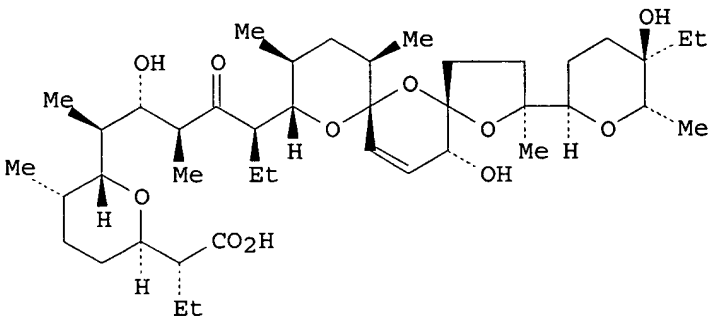
AB Title compds. are disclosed, namely I [A = X1A1X2, X2A1X1, 1,4-piperazinediyl; A1 = linear or branched C2-6 divalent aliphatic group with optional double or triple bond, Y, CH2YCH2 (Y = cyclopentanediyl or cyclohexanediyl), (un)substituted CH2C6H4CH2; X1 = O, S, SO, SO2, CH2, 1,4-piperazinediyl; X2 = O, S, CH2, OC6H4; B = CH:CH, CH:N, S, 1,2-C6H4; Het = (un)substituted mono-, di-, or tricyclic heterocyclyl; R4 = F, Cl, Br, iodo, (di)(alkyl)amino, OH, alkoxy, alkyl] and their stereoisomers and salts. The compds., being antagonists of leukotriene B4, are useful for treating inflammatory and allergic conditions such as asthma, ulcerative

colitis, psoriasis, and gastropathy induced by nonsteroidal antiphlogistics. For example, Pinner reaction of 4-[2-(2-benzothiazolyloxy)ethoxy]benzonitrile, by treatment with HCl and EtOH in CH2Cl2 at -15°, and ammonolysis of the precipitated crystalline imidate with NH3-saturated EtOH at reflux, gave title compound II as the HCl salt. I had Ki of 1-20 nM in an LTB4 receptor binding assay. Over 90 I are listed with m.p. data.

L26 ANSWER 45 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1987:211507 HCAPLUS
DOCUMENT NUMBER: 106:211507
TITLE: Ion transport and electrophysiology of the early proximal colon of rabbit
AUTHOR(S): Clauss, W.; Biehler, K. H.; **Schaefer, H.**; Wills, N. K.
CORPORATE SOURCE: Inst. Zoophysiol., Univ. Hohenheim, Stuttgart, D-7000, Fed. Rep. Ger.
SOURCE: Pfluegers Archiv (1987), 408(6), 592-9
CODEN: PFLABK; ISSN: 0031-6768
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Transepithelial transport of Na+, K+, and Cl- in the isolated initial segment (P1) of rabbit colon in vitro was studied by using radioisotopic tracer fluxes and electrophysiol. techniques. Like the rabbit descending colon, the proximal colon actively absorbs Na+ and Cl-; however, its transport systems are markedly different. In vivo, this segment absorbs K+, but active K+ secretion was observed in vitro. Unlike the descending colon, Na+ absorption is relatively insensitive to amiloride, and only a slight **inhibition** was obtained even at 1 mM concns. of this drug. Na+ and Cl- absorption appeared to be coupled (directly or indirectly), since the absorption of each ion was **inhibited** by the removal of the other. Serosal ouabain also **inhibited** Na+ and Cl- absorption and net K+ secretion. Unlike the descending colon, the proximal P1 segment did not have a net absorptive K+ transport system that was detectable in the presence of ouabain. Elec., the early proximal colon has a low transepithelial resistance compared to descending colon (RT = 133 Ω/cm2) but a larger short-circuit current (Isc = 178 μA/cm2). The transepithelial potential averaged -21 mV, in excellent agreement with values measured in vivo. The apical and basolateral membrane potentials averaged -21 mV and -42 mV, and intracellular K+ activity was 70 mM. The findings indicate active K+ uptake across the basolateral membrane and passive exit across the apical membrane. The basolateral membrane conductance may be a K+ conductance that is blockable by Ba+. It is likely that K+ transport normally occurs by both cellular and paracellular routes in this epithelium. Because of the numerous differences between this segment and the descending colon, the P1 segment of proximal colon apparently has a distinct function in colonic electrolyte transport.

L26 ANSWER 46 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1985:39549 HCAPLUS
DOCUMENT NUMBER: 102:39549
TITLE: Cationophore properties of the new polyether antibiotic salinomycin investigated in distal rabbit colon in vivo and in vitro
AUTHOR(S): **Schaefer, H.**; Clauss, W.; Hoernicke, H.
CORPORATE SOURCE: Inst. Zoophysiol., Univ. Stuttgart-Hohenheim, Stuttgart, D-7000/70, Fed. Rep. Ger.
SOURCE: Comparative Biochemistry and Physiology, Part A:

Molecular & Integrative Physiology (1984), 79A(3), 387-92
CODEN: CBPAB5; ISSN: 0300-9629
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB In the distal rabbit colon, salinomycin (I) [53003-10-4] (104 M) did not influence net water, Cl- or, Na+ absorption, but it decreased K+ secretion to zero and the transepithelial potential was decreased from -45 mV to -33 mV. I at 10-4 and 10-3 M applied to the mucosal side of the colon decreased the transepithelial potential from 18 mV to zero within 80 and 30 min, resp. I also affected the short-circuit current and the transepithelial conductance in a dose-dependent manner. The unidirectional 22Na fluxes were increased to 20 times the control values and the net Na transport was **inhibited** by I. Thus, I given in doses used as a coccidiostatic feed additive profoundly affected colon electrolyte transport.

L26 ANSWER 47 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1985:106108 HCAPLUS
DOCUMENT NUMBER: 102:106108
TITLE: Indalpine, a potent and selective 5-HT uptake blocker
AUTHOR(S): Le Fur, G.; Gueremy, C.; **Benavides, J.**; Malgouris, C.; Uzan, A.
CORPORATE SOURCE: Pharm. Lab., Groupe Rhone Poulenc Sante, Gennevilliers, Fr.
SOURCE: Advances in Biological Psychiatry (1984), 14(Serotonin Affective Disord.), 33-40, 1 plate
CODEN: ABPSD5; ISSN: 0378-7354
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 5-HT [50-67-9] uptake by rat brain in vitro was **inhibited** by indalpine (I) [63758-79-2]; I showed no affinity for catecholamine or amino acid uptake systems. Twice daily administration of I (10 mg/kg, i.p.) during a 14 day period did not downregulate β, 5-HT1, or 5-HT2 receptors. Thus the therapeutic effect of I is not associated with downregulation of monoamine postsynaptic receptors. In binding studies, the **inhibition** of I binding to rat brain by tricyclic antidepressants paralleled their **inhibition** of 5-HT uptake. No correlation, however, was found between the **inhibition** of I binding and **inhibition** of noradrenaline uptake by antidepressants. I binding in rat brain was competitively **inhibited** by 5-HT. Pharmacol. studies of I binding sites in brain

suggest these sites may be located in 5-HT neurons. Thus, I is a potent 5-HT **reuptake** blocker characterized by a very high selectivity of action due to its affinity to presynaptic sites.

L26 ANSWER 48 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1975:69569 HCAPLUS
DOCUMENT NUMBER: 82:69569
TITLE: Estimation of enzyme activity in living epidermal cells
AUTHOR(S): Schalla, W.; Zesch, A.; **Schaefer, H.**
CORPORATE SOURCE: Rudolf-Virchow-Hosp., Free Univ., Berlin, Fed. Rep. Ger.
SOURCE: British Journal of Dermatology (1974), 91(5), 489-501
CODEN: BJDEAZ; ISSN: 0007-0963
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A method is described for measurement of cytoplasmic enzymes in intact cells of excised human epidermis. The method is suitable for determination of lactic dehydrogenase (I), malate dehydrogenase (II), pyruvate kinase (III), glutamate-oxalacetate transaminase, and NADP-dependent isocitrate dehydrogenase, but not of mitochondrial glutamate dehydrogenase and NAD-dependent isocitrate dehydrogenase. Ouabain **inhibited** activity of cellular but not of extracellular I, II, and III. Fluoromalate **inhibited** activity of both forms of II. The activity of I was higher under anaerobic than under aerobic conditions. The **app**. can be modified for determining enzyme activity in epidermis in situ, following removal of stratum corneum by tape stripping. Activity of I, but not of II, is significantly higher in psoriatic than in normal skin. Activity of both enzymes is reduced within 15 min by oral administration of prednisolone or i.v. administration of methotrexate.

L26 ANSWER 49 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1970:130964 HCAPLUS
DOCUMENT NUMBER: 72:130964
TITLE: Biochemical studies of psoriasis chemotherapy
AUTHOR(S): **Schaefer, H.**
CORPORATE SOURCE: Fed. Rep. Ger.
SOURCE: Archiv fuer Klinische und Experimentelle Dermatologie (1968), 237, 240-5
CODEN: AKEDAX; ISSN: 0300-8614
DOCUMENT TYPE: Journal
LANGUAGE: German
AB The **inhibitory** effect of Cignolin (I) and 6-hydroxy-1,3-benzoxathiol-2-one (II) on cutaneous enzymes was investigated. I **inhibited** glucose-6-phosphate dehydrogenase and reacted with NADPH. II **inhibited** glucose-6-phosphate dehydrogenase, glutamic-oxalacetic transaminase, malic dehydrogenase and leucine aminopeptidase, but not aldolase, lactic dehydrogenase, isocitric dehydrogenase, and glutathione **reductase**.

L26 ANSWER 50 OF 65 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1949:50774 HCAPLUS
DOCUMENT NUMBER: 43:50774
ORIGINAL REFERENCE NO.: 43:9108b-f
TITLE: Critique and procedure for cholinesterase determinations in blood
AUTHOR(S): **Schaefer, Hans**; Maier, Erich
SOURCE: Biochemische Zeitschrift (1949), 319, 420-38
CODEN: BIZEA2; ISSN: 0366-0753

DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB The hydrolysis of acetylcholine (ACh) in human blood under physiol. conditions, i.e., very small concns., is almost entirely due to cholinesterase of the erythrocytes and practically none to cholinesterase of the serum. Therefore, changes in serum cholinesterase values are physiologically without importance so long as the erythrocyte cholinesterase values are normal. It is important to bear clearly in mind that, wherever cholinesterase is diminished, the ACh liberated at any parasympathetic ending remains active for a longer than normal duration. As a result a vagotonus develops, or temporary predominant parasympathetic innervation. Of course, this hypothesis presupposes that the ACh measured is the ACh which is effective in the vegetative field upon which the parasympathetic acts. It always seemed more or less doubtful whether the serum cholinesterase represented such a reference. The motor end plate is definitely the place where ACh is liberated, as can be judged by its high local concentration It is not permissible thus to regard a decrease in serum cholinesterase as an indication of increased vagotonus. Besides, since the serum cholinesterase is presumably an unspecific pseudocholinesterase, its variations probably reflect changes in the composition of protein fractions rather than those in the vegetative hormonal system. But neither does the determination of erythrocyte cholinesterase reveal anything regarding the cholinergic transmission at the vegetative end organs. Certain kinetic constants must be measured to determine the cholinesterase activity of erythrocytes. This is done in the Warburg **app**. and from these detns. the relative cholinesterase concentration is calculated, as well as the mode
of binding of ACh and cholinesterase, and finally the equilibrium constant of the **inhibitory** reaction between cholinesterase and ACh. The cholinesterase concentration attains a min. at about 30 years of age.

L26 ANSWER 51 OF 65 MEDLINE on STN
ACCESSION NUMBER: 2005184964 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15816856
TITLE: Expression of human FE65 in amyloid precursor protein transgenic mice is associated with a reduction in beta-amyloid load.
AUTHOR: Santiard-Baron Dominique; Langui Dominique; Delehedde Maryse; Delatour Benoit; Schombert Brigitte; Touchet Nathalie; Tremp Gunter; Paul Marie-Francoise; Blanchard Veronique; Sergeant Nicolas; Delacourte Andre; Duyckaerts Charles; **Pradier Laurent**; Mercken Luc
CORPORATE SOURCE: Neurodegenerative Diseases Group, Aventis, Vitry-sur-Seine, France.
SOURCE: Journal of neurochemistry, (2005 Apr) Vol. 93, No. 2, pp. 330-8.
Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200505
ENTRY DATE: Entered STN: 9 Apr 2005
Last Updated on STN: 21 May 2005
Entered Medline: 20 May 2005
AB FE65 is an adaptor protein that interacts with the cytoplasmic tail of the amyloid precursor protein (**APP**). In cultured non-neuronal cells, the formation of the FE65-**APP** complex is a key element for the modulation of **APP** processing, signalling and

beta-amyloid (Abeta) production. The functions of FE65 in vivo, including its role in the metabolism of neuronal **APP**, remain to be investigated. In this study, transgenic mice expressing human FE65 were generated and crossbred with **APP** transgenic mice, known to develop Abeta deposits at 6 months of age. Compared with **APP** mice, **APP**/FE65 double transgenic mice exhibited a lower Abeta accumulation in the cerebral cortex as demonstrated by immunohistochemistry and immunoassay, and a lower level of **APP** -CTFs. The reduced accumulation of Abeta in **APP**/FE65 double transgenics, compared with **APP** mice, could be linked to the low Abeta42 level observed at 4 months of age and to the lower **APP** -CTFs levels. The present work provides evidence that FE65 plays a role in the regulation of **APP** processing in an in vivo model.

L26 ANSWER 52 OF 65 MEDLINE on STN
ACCESSION NUMBER: 91264881 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1646613
TITLE: Pharmacodynamics, pharmacokinetics and safety profile of the new platelet-activating factor antagonist apafant in man.
AUTHOR: Brecht H M; Adamus W S; **Heuer H O**; Birke F W; Kempe E R
CORPORATE SOURCE: Department of Medicine, Boehringer Ingelheim KG, Rhein, Germany.
SOURCE: Arzneimittel-Forschung, (1991 Jan) Vol. 41, No. 1, pp. 51-9.
Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199107
ENTRY DATE: Entered STN: 2 Aug 1991
Last Updated on STN: 2 Aug 1991
Entered Medline: 15 Jul 1991

AB Platelet-activating factor (PAF) is a unique phospholipid mediator with multifunctional properties. Evidence generated in experimental studies suggests that PAF plays a pathogenetic role in anaphylactic, inflammatory and immunogenic reactions. Apafant (WEB 2086, CAS 105219-56-5), a novel synthetic PAF receptor antagonist, was administered to a total of 101 healthy volunteers within 5 studies to investigate its pharmacologic activity, pharmacokinetic behaviour and safety profile. Pharmacologic activity was monitored by **inhibition** of 5 x 10(-8) mol/l PAF-induced platelet aggregation ex vivo. The following treatment schedules were studied: oral single dose 1.25 to 400 mg; oral multiple dose 100 mg t.i.d. over 7 days; i.v. infusion 0.5 to 50 mg (over 30 min); inhalative administration up to 1.0 mg. PAF induced platelet aggregation was virtually completely **inhibited** by single oral doses of 20 mg upwards, throughout during the multiple oral dose study, at all dose levels tested in the i.v. study and (significantly but not completely) at 0.5 and 1.0 mg in the inhalative study. Following oral administrations (capsules) apafant is absorbed rapidly (tmax 1 to 2 h), there is linear pharmacokinetics for the mean plasma concentrations of apafant measured by RIA as well as for the areas under the curve (AUCs). Approximately 60% of apafant is bound to plasma protein, the mean volume of distribution is 28 l, about 44% of an oral dose is excreted in the urine, the mean renal clearance is 192 ml/min. No accumulation of the drug occurred in

volunteers with normal kidney function. No clinically relevant drug related adverse events or changes in laboratory or vital parameters such as blood pressure, heart rate, respiratory rate and ECG were observed. (ABSTRACT TRUNCATED AT 250 WORDS)

L26 ANSWER 53 OF 65 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 90126142 EMBASE
DOCUMENT NUMBER: 1990126142
TITLE: Tumor necrosis factor (TNF) and endotoxin prime effects of PAF in vivo.
AUTHOR: **Heuer H.O.**; Letts G.; Meade C.J.
CORPORATE SOURCE: Department of Pharmacology, Boehringer Ingelheim, D-6507 Ingelheim/Rhein, Germany
SOURCE: Journal of Lipid Mediators, (1990) Vol. 2, No. SUPPL., pp. S101-S108. .
ISSN: 0921-8319 CODEN: JLMEEG
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 13 Dec 1991
Last Updated on STN: 13 Dec 1991

AB The purpose of the present study in NMRI mice was to investigate the action of platelet-activating factor (PAF) on mortality and **intestinal** transit velocity, the interaction of endotoxin or tumor necrosis factor (TNF) with the effect of PAF on these parameters and the effect of the PAF antagonist WEB 2086 on the endotoxin/TNF- and PAF-induced changes. PAF at a high dose (200 μg/kg i.v.) increased mortality and reduced transit velocity. This effect was **inhibited** by WEB 2086 (0.01 - 0.5 mg/kg i.p.) in a dose-dependent manner. Pretreatment with endotoxin (S. typhosa; 10 μg/kg i.v.) or TNF (40 μg/kg i.v.) enhanced the activity of PAF resulting in increased mortality and reduced transit velocity. This enhanced activity of PAF in the case of pretreatment with endotoxin or TNF occurred at doses at which PAF, endotoxin or TNF given alone did not significantly affect these parameters. The ability of endotoxin or TNF to enhance the effect of PAF was maximal, if the time delay between endotoxin and subsequent PAF administration was about 1 - 2 h. WEB 2086 (0.01 - 1 mg/kg i.p.) **inhibited** this priming in a dose-dependent fashion. These findings support suggestions of a role for PAF in endotoxin shock and TNF-associated shock-like syndrome.

L26 ANSWER 54 OF 65 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:210443 BIOSIS
DOCUMENT NUMBER: PREV200400213329
TITLE: Diphenylazetidinone derivatives, process for their preparation, medicaments comprising these compounds and their use.
AUTHOR(S): Glombik, Heiner [Inventor, Reprint Author]; Kramer, Werner [Inventor]; Flohr, Stefanie [Inventor]; Frick, Wendelin [Inventor]; **Heuer, Hubert** [Inventor]; Jaehne, Gerhard [Inventor]; Lindenschmidt, Andreas [Inventor]; **Schaefer, Hans-Ludwig** [Inventor]
CORPORATE SOURCE: Hofheim, Germany

ASSIGNEE: Aventis Pharma Deutschland GmbH, Frankfurt am Main, Germany
PATENT INFORMATION: US 6703386 20040309
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Mar 9 2004) Vol. 1280, No. 2. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Apr 2004
Last Updated on STN: 14 Apr 2004

AB Compounds of the formula I, for example, are disclosed, ##STR1## in which R1, R2, R3, R4, R5, and R6 independently of one another are (C0 -C30)-alkylene-L or are the meanings given in the description, and where L is shown connected to (C0 -C30)-alkylene as follows: ##STR2## where Rx, Ry, Rz have the meanings given in the description, and their physiologically acceptable salts. The compounds are suitable for use, for example, as hypolipidemics.

L26 ANSWER 55 OF 65 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:158029 BIOSIS
DOCUMENT NUMBER: PREV200600174128
TITLE: The squalene synthase **inhibitor** RPR 107393A reduces A beta peptide level in an **APP** transgenic mouse model.
AUTHOR(S): **Pradier, Laurent** [Reprint Author]; **Canton, Thierry**; Bouaiche, Zakia; Benoit, Patrick; **Benavides, Jesus**
CORPORATE SOURCE: Aventis Pharma, Vitry Sur Seine, France laurent.pradier@aventis.com
SOURCE: Neurobiology of Aging, (JUL 2004) Vol. 25, No. Suppl. 2, pp. S568. Meeting Info.: 9th International Conference on Alzheimers Disease and Related Disorders. Philadelphia, PA, USA. July 17 -22, 2004. Alzheimers Assoc. CODEN: NEAGDO. ISSN: 0197-4580.
DOCUMENT TYPE: Conference; (Meeting) Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Mar 2006
Last Updated on STN: 9 Mar 2006

L26 ANSWER 56 OF 65 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:156619 BIOSIS
DOCUMENT NUMBER: PREV200600172718
TITLE: The role of the tissue-type plasminogen activator in the course of amyloid accumulation.
AUTHOR(S): Cacquevel, Mathias [Reprint Author]; Cheenne, Simon; Castel, Herve; **Benavides, Jesus**; **Pradier, Laurent**; Vivien, Denis
CORPORATE SOURCE: Aventis Pharma, Vitry Sur Seine, France m.cacquevel@cyceron.fr
SOURCE: Neurobiology of Aging, (JUL 2004) Vol. 25, No. Suppl. 2, pp. S141. Meeting Info.: 9th International Conference on Alzheimers Disease and Related Disorders. Philadelphia, PA, USA. July 17 -22, 2004. Alzheimers Assoc.

CODEN: NEAGDO. ISSN: 0197-4580.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Mar 2006
Last Updated on STN: 9 Mar 2006

L26 ANSWER 57 OF 65 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:83632 BIOSIS
DOCUMENT NUMBER: PREV200300083632
TITLE: Diphenylazetidinone derivatives, process for their preparation, medicaments comprising these compounds and their use.
AUTHOR(S): Glombik, Heiner [Inventor, Reprint Author]; Kramer, Werner [Inventor]; Flohr, Stefanie [Inventor]; Frick, Wendelin [Inventor]; **Heuer, Hubert** [Inventor]; Jaehne, Gerhard [Inventor]; Lindenschmidt, Andreas [Inventor]; **Schaefer, Hans-Ludwig** [Inventor]
CORPORATE SOURCE: Hofheim, Germany
ASSIGNEE: Aventis Pharma Deutschland GmbH, Frankfurt am Main, Germany
PATENT INFORMATION: US 6498156 20021224
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Dec 24 2002) Vol. 1265, No. 4. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Feb 2003
Last Updated on STN: 6 Feb 2003
AB Compounds of the formula I, ##STR1## in which R1, R2, R3, R4, R5, and R6 have the meanings given in the description, and their physiologically acceptable salts. The compounds are suitable for use, for example, as hypolipidemics.

L26 ANSWER 58 OF 65 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:618139 BIOSIS
DOCUMENT NUMBER: PREV200200618139
TITLE: Effect of a newly developed specific bile acid reabsorption **inhibitor** on bile acid and lipoprotein metabolism in apoE*3-Leiden transgenic mice.
AUTHOR(S): Groenendijk, Martine [Reprint author]; Post, Sabine M. [Reprint author]; **Schaefer, Hans-Ludwig**; Kramer, Werner; Princen, Hans M. [Reprint author]
CORPORATE SOURCE: Gaubius Laboratory, TNO-Prevention and Health, Leiden, Netherlands
SOURCE: Hepatology, (October, 2002) Vol. 36, No. 4 Part 2, pp. 297A. print.
Meeting Info.: 53rd Annual Meeting on the Liver. BOSTON, MA, USA. November 01-05, 2002.
CODEN: HPTLD9. ISSN: 0270-9139.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Dec 2002
Last Updated on STN: 4 Dec 2002

L26 ANSWER 59 OF 65 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:7312 BIOSIS
DOCUMENT NUMBER: PREV200400000600
TITLE: Prevention of **cholestatic** hepatitis by bile-acid-**reuptake-inhibitors** in rat.
AUTHOR(S): Sauer, Peter [Reprint Author]; Kloeters-Plachky, Petra; Kramer, Werner; **Schaefer, Hans-Ludwig**; Rost, Daniel; Rudolph, Gerda; Stremmel, Wolfgang; Stiehl, Adolf
CORPORATE SOURCE: Heidelberg, Germany
SOURCE: Gastroenterology, (July 2002) Vol. 123, No. 1 Supplement, pp. 62-63. print.
Meeting Info.: Digestive Disease Week and the 103rd Annual Meeting of the American Gastroenterological Association. San Francisco, CA, USA. May 19-22, 2002. American Gastroenterological Association.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Dec 2003
Last Updated on STN: 17 Dec 2003

L26 ANSWER 60 OF 65 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:315418 BIOSIS
DOCUMENT NUMBER: PREV200300315418
TITLE: EXPRESSION OF HUMAN Fe65 IN NEURONS AND IN VIVO.
AUTHOR(S): Santiard-Baron, D. [Reprint Author]; Delatour, B.; Clark, A. [Reprint Author]; Schombert, B. [Reprint Author]; Touchet, N. [Reprint Author]; Bouaiche, Z. [Reprint Author]; Paul, M. F. [Reprint Author]; Duyckaerts, C.; **Pradier, L.** [Reprint Author]; **Benavides, J.** [Reprint Author]; Mercken, L. [Reprint Author]
CORPORATE SOURCE: Aventis Pharma, Vitry/seine, France
SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 624.4. http://sfn.scholarone.com. cd-rom.
Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Jul 2003
Last Updated on STN: 9 Jul 2003

AB FE65 is an adaptor protein that tightly binds to the cytoplasmic tail of the Amyloid Precursor Protein (APP). In cultured non-neuronal cells, the formation of the FE65-APP complex is a key element for the modulation of APP processing and signaling. In contrast, the function of FE65 in cultured neurons and in vivo remains to be determined. In this study, we generated double transgenic mice with neuronal expression of mutant APP and human FE65 under the control of the PDGF-B promoter (PDGF APP 695 (SDL) x PDGF FE65). Comparison of primary cultures of cortical neurons from double and single APP transgenic mice revealed that APPxFE65 neurons released more Amyloid beta-peptides in the conditioned medium than APPxWild type neurons. Our results are consistent with the data obtained in non-neuronal cells. The neuropathological status of the double

transgenic mice was evaluated during their life span (up to 18 months). These mice displayed a massive glial response as abundant reactive astrocytes were observed at 9 months throughout all cortical layers (4 out of 5 animals). On the contrary, gliosis was limited and mainly evidenced into the first cortical layer in single APP transgenic mice. This neuropathological event occurred several months before the appearance of amyloid plaques, which were observed from 18 months in the single APP transgenic mice. We hypothesize that the increased release of Amyloid beta-peptides, as observed in the APPxFE65 neurons, contributes to the reactive gliosis observed in the double transgenic mice.

L26 ANSWER 61 OF 65 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:292955 BIOSIS
DOCUMENT NUMBER: PREV200100292955
TITLE: Identification of the **intestinal cholesterol** transporter.
AUTHOR(S): Kramer, W. [Reprint author]; Glombik, H. [Reprint author]; Petry, S. [Reprint author]; **Heuer, H.** [Reprint author]; Corsiero, D. [Reprint author]; Girbig, F. [Reprint author]; Weyland, C. [Reprint author]
CORPORATE SOURCE: DG Metabolic Diseases Industriepark Hoechst, Aventis Pharma Deutschland GmbH, Gebaeude G 838, 65926, Frankfurt am Main, Germany
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology, (2001) Vol. 363, No. 4 Supplement, pp. R5. print.
Meeting Info.: 42nd Spring Meeting of the German Society for Experimental and Clinical Pharmacology and Toxicology. Mainz, Germany. March 13-15, 2001. German Society for Experimental and Clinical Pharmacology and Toxicology.
CODEN: NSAPCC. ISSN: 0028-1298.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Jun 2001
Last Updated on STN: 19 Feb 2002

L26 ANSWER 62 OF 65 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1997:512716 BIOSIS
DOCUMENT NUMBER: PREV199799811919
TITLE: Topological photoaffinity labeling of the rabbit ileal Na+/bile-salt-cotransport system.
AUTHOR(S): Kramer, Werner [Reprint author]; Wess, Guenther; Bewersdorf, Ulrike; Corsiero, Daniel; Girbig, Frank; Weyland, Claudia; Stengelin, Siegfried; Enhsen, Alfons; Bock, Klaus; Kleine, Horst; Le Dreau, Marie-Anne; **Schaefer, Hans-Ludwig**
CORPORATE SOURCE: Hoechst Marion Roussel, DG Metabolic Dis., D-65926 Frankfurt am Main, Germany
SOURCE: European Journal of Biochemistry, (1997) Vol. 249, No. 2, pp. 456-464.
CODEN: EJBCAI. ISSN: 0014-2956.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 1997
Last Updated on STN: 10 Dec 1997
AB For the investigation of the topology of the rabbit ileal Na+/bile-salt-cotransport system, composed of a 93-kDa integral membrane

protein and a peripheral 14-kDa bile-acid-binding protein (ILBP), we have synthesized photolabile dimeric bile-salt-transport **inhibitors** (photoblockers), G1-X-G2, where two bile acid moieties (G1 and G2) are tethered together via a spacer, X, and where one of the two bile acid moieties carries a photoactivatable group. These photoblockers specifically interact with the ileal Na+/ bile-salt-cotransport system as demonstrated by a concentration-dependent **inhibition** of (3H)cholyltaurine uptake by rabbit ileal brush-border membrane vesicles and by **inhibition** of photolabeling of the 93-kDa and 14-kDa bile-salt-binding proteins by 7,7-azo and 3,3-azo derivatives of cholyltaurine. Ileal bile-salt uptake was specifically **inhibited** by the photoblockers, which were not taken up themselves by the small **intestine** as demonstrated by in vivo ileal perfusion. Dependent on the photoblocker used several polypeptides in the molecular-mass range of 14-130 kDa were labeled. The cytoplasmically attached 14-kDa ILBP was significantly labeled only by **inhibitors** that are photoactivatable in bile acid moiety G1, suggesting that during binding and translocation of a bile-salt molecule by the ileal bile-salt-transport system the steroid nucleus gets access to the cytoplasmic site of the ileal brush-border membrane first. Photoaffinity labeling in the frozen state with the transportable 3,3-azo and 7,7-azo derivatives of cholyltaurine revealed a time-dependent increase in the extent of labeling of the 14-kDa and 93-kDa proteins, suggesting a labeling of these proteins from the cytoplasmic site of the ileal brush-border membrane. By photoaffinity labeling in the frozen state with the various photoblockers time-dependent changes in the extent of photoaffinity labeling of bile-salt-binding proteins were observed, demonstrating the possibility of topological analysis of the rabbit ileal Na+/bile-salt-cotransport system.

L26 ANSWER 63 OF 65 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1997:197782 BIOSIS
DOCUMENT NUMBER: PREV199799496985
TITLE: Synthesis and sar of trimeric bile acid reabsorption **inhibitors**: A new approach to lower **cholesterol**.
AUTHOR(S): Glombik, H.; Baringhaus, K.-H.; Boeger, G.; Enhsen, A.; Falk, E.; Friedrich, M.; Hoffmann, A.; Kramer, W.; **Schaefer, H. L.**; Stengelin, S.; Wess, G.
CORPORATE SOURCE: HMR TA Metabolism Research D-65926 Frankfurt, Germany
SOURCE: Abstracts of Papers American Chemical Society, (1997) Vol. 213, No. 1-3, pp. MEDI 108.
Meeting Info.: 213th National Meeting of the American Chemical Society. San Francisco, California, USA. April 13-17, 1997.
CODEN: ACSRAL. ISSN: 0065-7727.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 May 1997
Last Updated on STN: 2 May 1997

L26 ANSWER 64 OF 65 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1996:44690 BIOSIS
DOCUMENT NUMBER: PREV199698616825
TITLE: The ileal bile acid transporter: Molecular structure and specific **inhibitors**.
AUTHOR(S): Kramer, W. [Reprint author]; Wess, G.; Baringhaus, K.-H.;

Boeger, G.; Enhsen, A.; Falk, E.; Friedrich, M.; Glombik, H.; Hoffmann, A.; Neckermann, G.; Pittius, C.; **Schaefer, H.-L.**; Urmann, M.
CORPORATE SOURCE: Hoechst Aktiengesellschaft, D-65926 Frankfurt am Main, Germany
SOURCE: Biological Chemistry Hoppe-Seyler, (1995) Vol. 376, No. SPEC. SUPPL., pp. S70.
Meeting Info.: 120th Conference of the Gesellschaft fuer Biologische Chemie: Cell Biology and Molecular Basis of Liver Transport. Rottach-Egern, Germany. May 10-13, 1995.
CODEN: BCHSEI. ISSN: 0177-3593.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Feb 1996
Last Updated on STN: 3 Feb 1996

L26 ANSWER 65 OF 65 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1987:272087 BIOSIS
DOCUMENT NUMBER: PREV198784013126; BA84:13126
TITLE: EFFECTS OF GLIADIN PEPTIDES B1-B4 IN CELIAC DISEASE I. ORGAN CULTURE STUDIES.
AUTHOR(S): STALLMACH A [Reprint author]; BELITZ H-D; GELLERMANN B; **SCHAEFER H**; WIESER H; STERN M
CORPORATE SOURCE: UNIV-KINDERKLINIK, MARTINISTR 52, D-2000 HAMBURG, FRG
SOURCE: Journal of Pediatric Gastroenterology and Nutrition, (1987) Vol. 6, No. 3, pp. 335-340.
CODEN: JPGND6. ISSN: 0277-2116.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 19 Jun 1987
Last Updated on STN: 19 Jun 1987

AB Small **intestinal** organ culture was used as an in vitro system to study the enterotoxic effects of gliadin peptides. Measurement of enterocyte height proved to be a realiable and reproducible way of assessing mucosal change during organ culture. Enterocyte height decreases nonspecifically in normal cultured mucosal, whereas the height of enterocytes of celiac mucosa increases in vitro in controls. All the gliadin peptide fractions (B1, B2, B3, B4) that had been prepared by peptide-trypsin hydrolysis, ultrafiltration, and gel chromatography, equally **inhibited** the morphological increase of enterocyte height normally observed without gliadin in untreated celiac mucosa. Electrophoretic studies and amino acid analysis of B1-B4 revealed similarity between gliadin fractions with quantitative differences in molecular weight distribution of the peptide components. Our studies suggest that organ culture assessed by morphometry is a suitable model for the investigation of toxic peptides of gliadin in celiac disease. In the future, pure gliadin peptides will have to be examined.